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Health and Environmental Effects Profile for Acrolein

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16. ABSTRACT

The Health and Environmental Effects Profile for acrolein was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Acrolein has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for acrolein is 1.09 mg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for acrolein is 10.

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September 1985

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR ACROLEIN

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

The first draft of this document was prepared by Syracuse Research Corporation under Contract No. 68-03-3112. This document was subsequently reviewed and revised by ECAO-Cincinnati and the Carcinogen Assessment Group, the Exposure Assessment Group and the Reproductive Effects Assessment Group of the Office of Health and Environmental Assessment.

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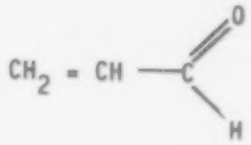
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
BOD	Biochemical oxygen demand
CS	Composite score
DENA	Diethylnitrosamine
DNA	Deoxyribonucleic acid
i.p.	Intraperitoneal
i.v.	Intravenous
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
NADPH	Nicotinamide adenine dinucleotide phosphate
ppm	Parts per million
RNA	Ribonucleic acid
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
s.c	Subcutaneous
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weight average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Acrolein is the common chemical name, but the compound is also known by the synonyms 2-propenal, acrylaldehyde, allyl aldehyde, acrylic aldehyde, acraldehyde, prop-2-en-1-al, and 2-propen-1-one. The structure, molecular weight and empirical formula for acrolein are as follows:



Molecular weight: 56.06

Empirical formula: C_3H_4O

The Chemical Abstract Service (CAS) Registry number for acrolein is 107-02-8.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

When pure, acrolein is a colorless volatile liquid with a pungent odor. (Hess et al., 1978; Verschueren, 1983). The odor can be highly disagreeable and choking (U.S. EPA, 1978a). Acrolein is soluble in many organic liquids such as alcohol, ether and acetone. Selected physical properties of acrolein are listed below:

Melting point:	87.0°C	Hess et al., 1978
Boiling point (760 mm Hg):	52.7°C	Union Carbide, 1979
Specific gravity:	0.8427 (20/20°C)	Union Carbide, 1979
Refractive index:	1.4013 (20°C)	Hess et al., 1978
Vapor pressure:		
at 20°C	220 mm Hg	Union Carbide, 1979
at 25°C	269 mm Hg	Callahan et al., 1979
at 30°C	330 mm Hg	Verschueren, 1983

Water solubility:		
at 20°C	20.8% by weight	Union Carbide, 1979
at 20°C	200,000 ppm	Kenaga, 1980
at 25°C	400,000 ppm	OHM/TADS, 1985
Log octanol/water partition coefficient K_{ow}:	0.09	Callahan et al., 1979
	0.01	Hansch and Leo, 1981
	0.009	Mabey et al., 1981
Ionization constant:	not environmentally relevant	Mabey et al., 1981
Conversion factor (air):	1 mg/m³ = 0.43 ppm 1 ppm = 2.3 mg/m³	Verschueren, 1983
Henry's Law Constant: at 20°C	7.8×10^{-5} atm-m³/mole (calculated)	

Acrolein polymerizes spontaneously with the polymerization promoted by ultraviolet radiation, alkaline materials and various other catalysts (Hess et al., 1978). It undergoes a variety of chemical reactions including reactions typical of the aldehyde function. Reduction of the aldehyde forms allyl alcohol, while oxidation of the aldehyde produces acrylic acid.

1.3. PRODUCTION DATA

Currently, acrolein is manufactured as an end-use product and as an unisolated intermediate in the production of acrylic acid. Union Carbide at Taft, LA, is the only domestic manufacturer that produces acrolein as an end-use product (SRI, 1984). The capacity of the Union Carbide facility is 60 million pounds/year but is readily expandable to 120 million pounds/year (Hess et al., 1978). In addition to Union Carbide, the acrylic acid manufacturers are (SRI, 1984): Badische (Freeport, TX), Celanese (Clear Lake, TX) and Rohm and Haas (Deer Park, TX). From 1959-1980, Shell Chemical (Norco, TX) produced acrolein for captive consumption in glycerin manufacture; however, Shell has closed this facility (CMR, 1981).

Production data available from the Public portion of U.S. EPA TSCA Production File (U.S. EPA, 1977) is listed in Table 1-1. In 1974, U.S. production of acrolein as an end-use product was ~61 million pounds with ~99-150 million pounds produced as an unisolated intermediate during acrylic acid production (IARC, 1979). In 1983, 733 million pounds of acrylic acid were produced domestically (USITC, 1984), which would require ~0.7 billion pounds of acrolein intermediate.

Acrolein is manufactured through the air oxidation of propylene (Hess et al., 1978); by following the reaction:

$$CH_3CH{=}CH_2 + O_2 \text{ ----> } CH_2{=}CHCHO + H_2O$$

1.4. USE DATA

The largest market for acrolein as an end-use product is the production of methionine, a protein supplement used in poultry feeds (Hess et al., 1978).

Significant amounts of acrolein are used to produced glutaraldehyde, a crosslinking agent for proteins and polyhydroxy compounds (Hess et al., 1978). Glutaraldehyde is produced by Union Carbide in Institute, WV (SRI, 1984). The dimer of acrolein is prepared by the thermal reaction of acrolein and hydrolysis of the dimer yields 2-hydroxyadipaldehyde which is used as a crosslinking agent to impart water resistance. Acrolein dimer is also used to make cotton crease-proof and to harden image-receiving layers for the azo dye-developer transfer process (Hess et al., 1978). Acrolein and butadiene are used as starting materials to produce Union Carbide's ERL-4221 bis-epoxide which is used to make electrical insulators (Hess et al., 1978). Acrolein is also used commercially as an intermediate to produce the vitamin niacin and to produce various epoxides and resins (Hess et al., 1978). Acrolein polymers, however, have no commercial applications as yet.

TABLE 1-1

Production Data from the 1977 U.S. EPA TSCA Production File

Producer (Location)	Type of Producer	1977 Production Range
Monsanto		
(Texas City, TX)	Manufacturer	0.1-1.0 million lbs.
(Alvin, TX)		none
Union Carbide		
(Hahnville, LA)	Manufacturer	confidential
Shell Chemical		
(Norco, LA)	Manufacturer	10-50 million lbs.
Hydron Laboratories		
(New Brunswick, NJ)	Manufacturer	under 1,000 lbs.
Ugine Kuhlmann of Amer.		
(Bergen, NJ)	Importer	confidential

Acrolein is used directly as an industrial antimicrobial agent (Trotz and Pitts, 1981; Hess et al., 1978) and at a concentration of 0.4-0.6 ppm, it is an effective slimicide in paper manufacturing. Jet fuels and distillate fuels can be protected from microorganisms by addition of acrolein. In the subsurface injection of waste waters, the addition of 6-10 ppm acrolein controls microbe growth in feed lines thereby preventing plugging and corrosion (Hess et al., 1978). The growth of algae, aquatic weeds, and mollusks in recirculating process water systems can be controlled by acrolein.

Acrolein is the active ingredient ($\geq$85% by wt.) in the aquatic herbicide Aqualin® which has been marketed by Shell Chemical (WSSA, 1979; Peters and Hood, 1967) for herbicide control weeds and algae in lakes, irrigation canals and drainage ditches.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The fate of acrolein in the environment depends upon the ability of the compound to undergo chemical, photochemical and biological reactions and to transport or partition from one environmental matrix into another.

2.1. WATER

2.1.1. Reactions With Water. Acrolein contains no hydrolyzable groups that lead to environmental transformations (Callahan et al., 1979; Mabey et al., 1981). A primary reaction of acrolein in aqueous solution is hydration to p-hydroxypropionaldehyde (Geyer, 1962); however, this process is not a hydrolytic process since the reaction is reversible (Callahan et al., 1979):

$$CH_2 = CHCHO + H_2O \rightleftharpoons HOCH_2CH_2CHO$$

Similarly, the polycondensation of acrolein in the presence of water is not a hydrolysis process since it is also potentially reversible (Callahan et al., 1979).

Burczyk et al. (1968) studied the kinetics of reversible hydration of acrolein to form p-hydroxypropionaldehyde in distilled water and calculated a pseudo-first order rate constant of 0.032 day^{-1} for the hydration; the calculated half-life is 21 days. The equilibrium constant for the hydration indicates that acrolein will be ~95% in the hydrated form once equilibrium is established (Callahan et al., 1979). It has been suggested that the hydration reaction occurs at a faster rate than indicated by Burczyk et al. (1968) (Mabey et al., 1981; Bowmer and Higgins, 1976; Bowmer et al., 1974).

2.1.2. Oxidation. Mabey et al. (1981) estimated the rate constants for the reaction of acrolein with singlet oxygen ($^1O_2$) and peroxy radical ($RO_2\cdot$) to be 1×10^7 M^{-1} hr^{-1} and 3.4×10^3 M^{-1} hr^{-1}, respectively. Assuming $^1O_2$ and $RO_2\cdot$ concentrations in natural sunlit

waters to be $1x10^{-12}$M and $1x10^{-9}$M (Mabey et al., 1981), respectively, respective halflives of 7.9 and 23.3 years are calculated, indicating no environmental importance.

2.1.3. Photolysis. Experimental photolysis rate data regarding acrolein in aqueous solution were not located in the available literature as cited in the Appendix. The ultraviolet spectrum of acrolein in hexane solvent shows moderate absorption in the wavelength range of 290-390 nm (Mabey et al., 1981) indicating a potential for photolysis; however, the hydration of acrolein in water destroys the chromophores that absorb light thereby limiting the effective potential for direct photolytic transformation (Mabey et al., 1981). Pertinent data regarding photosensitized photodegradation of acrolein were not located in the available literature as cited in the Appendix.

2.1.4. Microbial Degradation. Stover and Kincannon (1983) studied the biodegradation of acrolein in an activated sludge system using reactor residence times of 2-6 days. In terms of a 5-day BOD, acrolein removal efficiency was found to be 95.6-97.7%, indicating significant degradation due to microbes.

Tabak et al. (1981) studied the biodegradability of 114 organic priority pollutants (included in the U.S. EPA Consent Decree list) in an effort to ascertain the extent of microbial degradation and to determine the acclimation periods. The test method used was a static-culture flask-screening procedure using BOD dilution water and a settled domestic wastewater as microbial seed; 28 days of incubation consisted of a 7-day static incubation followed by 3 weekly subcultures. Acrolein was easily degraded with rapid adaption and acclimatization by the microbiota; at concentrations of 5 and 10 ppm, 100% of the acrolein was biodegraded within the first 7-day period.

Other studies have also reported that acrolein is biotransformed effectively in activated sludge (Wierzbicki and Wojcik, 1965; Larson, 1967; Hultman, 1982). In contrast, Bridie et al. (1979a) found no BOD removal of acrolein in 5-day BOD dilution tests using an effluent from a biological sanitary waste treatment plant as a microbial seed. Oberton and Stack (1957) observed no BOD removal of acrolein in a sewage seed noting that acrolein was toxic to the sewage microorganisms at the concentrations used (as low as 1.5 ppm); however, acrolein did respond slightly to acclimatization exhibiting a 5-day BODT of 30%.

Bowmer and Higgins (1976) examined the rate of disappearance of acrolein from natural irrigation water and from the same natural water to which thymol was added to suppress biological activity. The half-life in the pure natural water was 29 hours compared with 43 hours in the thymol-treated water. The results suggest that biotransformation does occur.

2.1.5. Transport

2.1.5.1. **VOLATILIZATION** -- Experimental data generated by Bowmer et al. (1974) and Bowmer and Higgins (1976) suggest that acrolein volatilization from water, particularly in turbulent flowing water, may be environmentally significant (Section 2.1.6.). The Henry's Law Constant for acrolein, calculated at 20°C from the water solubility (208,000 ppm) and vapor pressure (220 mm Hg), is 7.8×10^{-5} atm-m³/mole indicating that volatilization is significant in all natural bodies of water, although it may not be rapid (Lyman et al., 1982).

2.1.5.2. **ADSORPTION** -- No data are available to assess the importance of acrolein sorption to sediments. The high water solubility and low octanol/water partition coefficient of acrolein suggest that sorption is not a significant process in aquatic systems (Callahan et al., 1979).

2.1.5.3. BIOACCUMULATION -- Barrows et al. (1980) examined the bioaccumulation of acrolein in Bluegill Sunfish in a continuous-flow system in which the fish were exposed to a mean acrolein concentration of 13.1 µg/ℓ for 28 days. A Maximum BCF of 344 was determined for acrolein; however, this BCF may be an overestimate of the actual amount of acrolein in the tissue due to the test methodology which utilized ^{14}C-acrolein and monitored the radio-label. After 28 days the radio-label remaining in the fish may have represented acrolein metabolites.

Based on the water solubility of acrolein and using regression equations, Kenaga (1980) estimated the BCF for acrolein to be 0.6. A BCF can be estimated from the octanol/water partition coefficient (K_{ow}) using the following equation (Veith et al., 1980): Log BCF = 0.76 Log K_{ow} - 0.23. For acrolein (Log K_{ow} = -0.01), the BCF value of 0.6 is also calculated. These estimated BCF values suggest that the bioaccumulation of acrolein in aquatic systems will not be significant; however, the experimentally determined maximum BCF (Barrows et al., 1980) indicates a potential for moderate bioaccumulation.

2.1.6. Persistence. WSSA (1979) reported that the resultant average persistence in water of acrolein herbicide used at recommended rates will be 2-3 days depending on the water temperature.

Bowmer et al. (1974) studied the loss of acrolein by degradation and volatilization from sealed bottles and tanks of water. The amounts of acrolein dissipated after 8 days were 34% from the tank and 16% from bottles. The rate of disappearance of acrolein in the tank at a pH of 7.2 was 0.83 day^{-1}, which corresponds to a half-life of 0.84 days. Loss by volatilization from the tank was ~10% in 6.7 days; however, the lack of turbulence in

the tank was thought to have minimized volatility losses considerably. The authors suggested that hydration of the acrolein was the primary degradation pathway.

Bowmer and Higgins (1976) examined the fate of acrolein in buffered water solutions and in natural channel waters. In the buffered solutions (pHs of 5.4, 7.0 and 8.4), 92% of the initial acrolein (10 ppm) was dissipated in 12.5 days of incubation; while 100% was dissipated in 12.5 days in the natural water at initial acrolein concentrations of 6.1, 17.5 and 50.5 ppm. As noted in Section 2.1.4., part of the acrolein degradation in natural water can be attributed to microbial decomposition. An 8- to 10-fold increase in observed dissipation rates was observed in flowing water channel studies, suggesting major losses to volatilization.

2.2. AIR

2.2.1. Chemical Removal Processes. The atmospheric chemical removal processes include reaction with hydroxyl radicals, reaction with ozone, reaction with other radicals and photolytic transformations (Cupitt, 1980). Table 2-1 lists rate constants for the reaction of acrolein with $OH^{\cdot}$ radicals and with atomic oxygen $O(^3P)$. Removal by $OH^{\cdot}$ radicals is extremely significant with average atmospheric half-lives calculated to be 0.18-0.42 days. Products of the reaction of acrolein with OH radicals include CO, formaldehyde, glycoaldehyde, and, in the presence of nitrogen oxides, peroxynitrate and nitric acid (Edney et al., 1983). Removal by $O(^3P)$, however, is not significant; reaction products include acetylene and ethylene (Cadle et al., 1972).

TABLE 2-1

Reaction Rate Constants for Acrolein with OH Radicals and O(³P)

Reaction with	Rate Constant (cm^3/molecule-sec)	Temperature	Calculated Half-Life in Atmosphere*	Reference
OH	1.9×10^{-11}	25°C	0.42 days	Kerr and Sheppard, 1981
OH	2.8×10^{-11}	25°C	0.29 days	Maldotti et al., 1980
OH	4.4×10^{-11} (theoretically calculated)	NR	0.18 days	Cupitt, 1980
OH	3.45×10^{-11}	NR	0.23 days	Edney et al., 1983
O(³P)	2.75×10^{-13}	25°C	3.2 years	Cadle et al., 1972
O(³P)	4.9×10^{-13}	23°C	1.5 years	Gaffney et al., 1975

*Assuming average atmospheric OH· concentration of 10^6 molecules/cm^3 and O(³P) concentration of 2.5×10^4 molecules/cm^3.

NR=not reported

Cupitt (1980) theoretically calculated the rate constant for the reaction of acrolein with ozone to be 4×10^{-18} cm^3/molecule-sec. Assuming an average atmospheric ozone concentration of 10^{12} molecules/cm^3, a half-life of ~2 days can be calculated.

Aldehydes absorb sunlight and undergo direct atmospheric photolysis (NRC, 1982). The major vapor-phase photolysis products of acrolein at 313 nm are CO and ethylene, with acetylene, butadiene and CO_2 as minor products (Coomber and Pitts, 1969); the quantum yields of CO and ethylene (0.005 and 0.003, respectively) suggest that direct photolysis of acrolein will not be rapid (Callahan et al., 1979). Osborne et al. (1962) found that the quantum yields of ethylene and CO_2 were not >0.015 and 0.005, respectively. In an environmental photolysis chamber, Maldotti et al. (1980) observed no detectable photolysis of an acrolein-air mixture after 4 hours of irradation.

2.2.2. **Physical Removal Processes.** Cupitt (1980) indicated that physical removal of acrolein from the atmosphere is unlikely to be significant; however, Grosjean and Wright (1983) and Seki et al. (1977) detected acrolein in rainwater, suggesting that this removal mechanism may significant.

2.3. SOIL

Pertinent data regarding the chemical or microbial degradation of acrolein in soil were not located in the available literature as cited in the Appendix. As noted in Section 2.1.4., however, microbial transformation does occur in waters.

The high water solubility and low octanol/water partition of acrolein suggest that the compound may be leached readily in many types of soil. Based on the water solubility and using a regression equation, Kenaga (1980) predicted the K_{oc} for acrolein to be 5. Prediction of K_{oc} from

molecular topology and quantitative structure-activity relation analysis (Sabljic, 1984) yields a K_{oc} value of 32. Both K_{oc} predictions suggest that acrolein will be highly mobile in soil.

2.4. SUMMARY

Acrolein exposed to sunlit atmospheres is decomposed rapidly by reaction with hydroxyl radicals with a half-life in an average atmosphere of 0.18-0.42 days. Reaction with ozone may also contribute to the atmospheric depletion of acrolein. Direct photolysis, however, does not appear to be significant in relation to $OH^{\cdot}$ radical reaction. The presence of acrolein in rainwater samples suggests that dissolution may also contribute to the removal of acrolein from air.

In aquatic media, acrolein undergoes a reversible hydration reaction rather than hydrolysis to produce p-hydroxypropionaldehyde which is not susceptible to direct photolysis in water. The chemical oxidation of acrolein by singlet oxygen or $RO_2\cdot$ radicals does not appear to be important in aquatic environments. Acrolein appears to be susceptible to microbial degradation in water. The calculated Henry's Law Constant for acrolein, 7.8×10^{-5} atm-m^3/mole, suggests that volatilization from water is environmentally significant, but not rapid. Based on water solubility data and the octanol/water partition coefficient, acrolein is not expected to bioaccumulate in aquatic organisms, however, the experimentally determined maximum bioconcentration factor of 344 in Bluegill Sunfish (Barrows et al., 1980) indicates a potential for moderate bioaccumulation. Acrolein is not expected to be a persistent aquatic compound.

In soil estimation methods suggest that acrolein is readily susceptible to leaching.

3. EXPOSURE

3.1. WATER

Acrolein can enter the aquatic environment through industrial discharge and as a result of its use as an aquatic herbicide (U.S. EPA, 1980).

Acrolein has been detected in raw sewage in two sewage treatment plants in metropolitan Chicago at concentrations ranging from 216-825 ppb (Lue-Hing et al., 1981); concentrations in final effluents were below 100 ppb. Analysis of municipal effluents of Dayton, OH showed the presence of acrolein in 6/11 samples, with concentrations ranging from 20-200 ppb (U.S. EPA, 1980).

Grosjean and Wright (1983) detected acrolein, in combination with acetone (at a concentration of 50 ppb.), in rainwater sampled from Los Angeles, CA. Seki et al. (1977) detected acrolein (no concentration reported) in Japanese rainwater.

Cole et al. (1984) reported preliminary findings of the U.S. EPA's Nationwide Urban Runoff Program which was designed to evaluate priority pollutants in urban stormwater runoff, however, preliminary monitoring of acrolein was inconclusive as the sampling methodology was not appropriate.

Data for acrolein available from the gross analysis of the U.S. EPA's STORET Data Base are given in Table 3-1.

3.2. FOOD

Acrolein can be present in trace amounts in foods (U.S. EPA, 1980) and it has been detected in the following foods or food components (IARC, 1979): sugar-cane molasses, souring salted pork, the fish odor of cooked horse mackerel, the volatiles from white bread, the volatile components of raw chicken breast muscle, the volatiles from ripe arctic bramble berries, and the products from heating fats.

TABLE 3-1

U.S. EPA STORET Data Base Gross Analysis for Acrolein

Medium	No. Observations	Concentration		
		Maximum	Minimum	Mean
Water	3606	$1x10^6$ µg/ℓ	0 µg/ℓ	1240 µg/ℓ
Sediment (dry weight)	648	10000 µg/kg	0 µg/kg	1336 µg/kg
Fish tissue (wet weight)	549	2000 mg/kg	0 mg/kg	37 mg/kg

3.3. INHALATION

Acrolein is emitted to the atmosphere through auto and diesel exhaust, from forest fires and tobacco smoke, and from manufacturing and use facilities (Graedel, 1978; NRC, 1982). Acrolein has been detected in the exhaust gases from a passenger car diesel engine in concentrations of 0.2-0.3 ppm (Smythe and Karasek, 1973). In gasoline engine exhaust from cars without catalytic converters, acrolein may account for 2.6-9.8 mole% of the aldehyde portion of the exhaust while in cars with catalytic converters acrolein may account for 0-0.4 mole% (NRC; 1982). Acrolein concentrations of 0.2-5.3 ppm have been detected in exhaust from simple hydrocarbon fuels (Lloyd, 1978), while wood burning in fireplaces can emit 0.021-0.132 grams acrolein per kilogram wood (Lipari et al., 1984). Acrolein is also emitted in coal mine combustion products (Hartstein and Forshey, 1974) and in combustion products from burning polyethylene (Hodgkin et al., 1982). Cigarette smoke can emit 0.7 mg acrolein per cigarette (NRC, 1982). Acrolein is produced and emitted to the air when fats, oils and glycerols are heated to high temperatures (Johnstone and Miller, 1960); this may have importance for overheating of food materials.

Acrolein can also be formed in the atmosphere by the photooxidation of 1,3-butadiene (Maidotti et al., 1980; Shimada et al., 1978; Carassiti et al., 1980).

The NRC (1982) has reported the following air monitoring data for acrolein:

Los Angeles, CA (July, 1960-November, 1961): 1-14 ppb

Huntington Park, CA (August-November, 1968): 0-8 ppb

El Monte, CA (August-November, 1968): 0-8 ppb

Grosjean and Fung (1984) monitored the carbonyls present in Los Angeles air in the mornings between September 29 and November 13, 1982; the combination

of acrolein, acetone and propanol was identified in the concentration range of 1-54 ppb. The average acrolein concentration monitored in Los Angeles during September-November, 1961 was 7 ppb (Altshuller and McPherson, 1963).

Brodzinsky and Singh (1982) reported that 19 air samples taken in Edison, NJ had a mean concentration of 310 ppt while 42 air samples from Los Angeles, CA had a mean concentration of 6.9 ppb. Perry (1972) detected acrolein at a level of 0.14 mg/m^3 (60 ppb) in an atmospheric grab sample taken near an oil fire.

3.4. DERMAL

Pertinent data regarding dermal exposure to acrolein were not located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Egle (1972) exposed anesthetized dogs to acrolein concentrations of 0.4-0.6 mg/ℓ for 1-3 minutes by inhalation (ventilatory rate=6-20/minute). Of the inhaled acrolein 81-84% was retained, being taken up more readily by the upper respiratory tract.

Acrolein is an extremely reactive aldehyde, producing reactions at epithelial surfaces that would tend to prevent passage into the interior of the body (Brabec, 1982).

4.2. DISTRIBUTION

Distribution studies using oral exposure could not be located in the available literature as cited in the Appendix. Munsch et al. (1974) injected rats by the intraperitoneal route with 3.36 mg/kg ^{3}H-acrolein. These rats had been partially hepatectomized 70 hours previously. Twenty-four hours post- injection, 88.66, 3.13, 1.72, 0.94 and 0.56% of the radioactivity was found in acid-soluble, lipid, protein, RNA and DNA fractions of the liver, respectively. RNA and DNA binding remained constant, but protein binding increased 70 percent during the first 24 hours.

4.3. METABOLISM

Acrolein is highly reactive due to the presence of a carbon-carbon double bond and can be readily oxidized to organic acids that can serve as substrates for fatty acid oxidation pathways and also be shunted into the Kreb's cycle, by acetyl-CoA. The oxidation of aldehydes is catalyzed by aldehyde dehydrogenases located in the brain, red blood cells. liver, kidney, heart and placenta (Brabec, 1982). Aldehyde dehydrogenase thought to reside in the mitochondrion, requires NAD^{+} and reduced glutathione, but is strongly inhibited by sulfhydryl binding agents. The reaction of

aldehydes with glutathione produces thiohemiacetals, and glutathione condensation products have been isolated from urine of animals fed acrolein. Low pH encountered in the upper gastrointestinal tract may rapidly convert acrolein to saturated alcohol compounds (U.S. EPA, 1980), with the primary product being β-propionaldehyde. Rat liver mitochondrial preparations were unable to oxidize acrolein (Smith and Packer, 1972). Pietruszko et al. (1973) found that acrolein is a substrate for alcohol dehydrogenases taken from human and horse liver, and from yeast, after incubation together in vitro. In rats, subcutaneously administered acrolein was found to be converted to 3-hydroxypropylmercapturic acid (Kaye and Young, 1972; Kaye, 1973).

Giles (1979) reported that acrolein undergoes a complex reaction with glutathione in vitro producing a number of products, the major product being S-(3-hydroxypropyl) glutathione, which can be further metabolized to 3-hydroxypropylmercapturic acid.

Draminski et al. (1983) proposed a new pathway of acrolein metabolism in rats. Ten female Wistar rats were given 10 mg/kg of acrolein in a single oral administration and their urine was analyzed for metabolites. The major metabolites identified were S-carboxyethylmercapturic acid (S-carboxyethyl-N-acetyl-cysteine) and S-(propionic acid methyl ester) mercapturic acid. Another unidentified metabolite was found in expired air. These authors suggest that acrylic acid and methyl acrylate are intermediates in acrolein metabolism. The possible metabolic pathway is as follows: 1; acrolein is metabolized to either acrylic acid or by glutathione to S-glutathione to S-formylethylmercapturic acid, 2; acrylic acid is metabolized to methyl acrylate, which in turn is metabolized by glutathione to S-(propionic acid methylester) mercapturic acid; 3; S-formylethylmercapturic acid is further

changed to either S-hydroxypropylmercapturic acid or S-carboxyethylmercapturic acid; and 4; S-carboxyethylmercapturic acid is then converted into S-(propionic acid methylester)-mercapturic acid.

Hepatic microsomal binding and hepatic microsomal metabolism of [^{14}C]acrolein was investigated by Marinello et al. (1984). Covalent binding between [^{14}C]-acrolein and cytochrome P-450 occurred in liver microsomes and an epoxide, capable of binding covalently to proteins was observed. Glutathione, a compound containing free sulfhydryl groups, was the most potent in blocking the binding of [^{14}C]-acrolein (90% inhibition) athough cysteine was equally effective. N-acetylcysteine was less effective in preventing binding and lysine was only marginally effective. Binding was substantially enhanced in the presence of NADPH, suggesting that binding was metabolism-dependent and that a metabolite of acrolein was also binding to the microsomes The presence of mixed function oxidase inhibitors SKF-525A (1 mM) and metyrapone abolished the differences observed with and without NADPH. Marinello et al. (1984) concluded that acrolein binds to cytochrome P-450 by alkylation of sulfhydryl groups located in the apoprotein. They also noted that in the presence of NADPH and mixed function oxidase, acrolein is capable of further metabolism to a reactive metabolite, presumably an alkeneoxide that alkylates proteins in microsomes.

Acrolein has been found as a metabolite in a variety of biochemical processes including degradation of spermine, allyl alcohol and the antitumor agent, cyclophosphamide. (U.S. EPA, 1980).

4.4. EXCRETION

Twenty-four hours after a single s.c. injection of acrolein, the urine of rats contained 10.5% of the administered dose as the metabolite 3-hydroxypropylmercapturic acid (Kaye and Young, 1972; Kaye, 1973).

5. EFFECTS

5.1. CARCINOGENICITY

The following discussion of carcinogenicity has been excerpted from U.S. EPA (1982). The few studies reported in the literature regarding the carcinogenicity of acrolein are described below. Steiner et al., (1943) used "partly inbred albinos" from the author's own mouse stock. The protocol is presented in Table 5-2. The experiment was terminated at 24 months. Heated sesame oil injected subcutaneously produced three spindle cell sarcomas in 24 months. No sarcomas were noted in the acrolein-treated group.

In another study, Salamon and Roe (1956) used S strain mice (sex not specified). The protocol is presented in Table 5-1. Mice were examined weekly for papillomata. When a mouse died, a record was made of all malignant and benign tumors. At the end of the croton oil treatment, all mice were killed and examined postmortem for lung adenomata and other tumors. No significant differences were noticed between experimental and control groups.

A long-term inhalation study performed by Feron and Kruysse (1977) in Syrian golden (Mesocriceuts auratus) male and female hamsters is described below. The purposes were to study 1) the effect of chronic exposure to acrolein vapor, and 2) the possible significance of this aldehyde as a cofactor in respiratory carcinogenesis. The animals were about 6 weeks old when the experiment was started. Male and female hamsters, 252 of each sex, were evenly distributed according to sex and body weight over two exposure chambers one of which was a control chamber in which the animals were exposed to filtered and conditioned air, the other a test chamber in which acrolein vapor was added to the air supply. Both the hamsters in the control chamber and those in the test chamber were divided according to

TABLE 5-1

Description of Experimental and Control Groups*

Group	Female	Male	Total	Mode, Level, and Frequency of Administration
1	0	18	18	50 mg cholesterol in 0.5 cc sesame oil, injection subcutaneously in the interscapular region; 5 injections, 4 weeks apart
2	15	0	15	0.2 mg acrolein in 0.1 cc sesame oil, injection at weekly intervals for 24 weeks
3	15	16	31	0.5 cc sesame oil heated to 350°C, cooled, and injected at three 4-week intervals

*Source: Steiner et al., 1943

TABLE 5-2

Description of Experimental and Control Groups[a]

Group	Control[b]	Experimental[c]	Tumor Type
Treatment	Croton oil	Acrolein/croton oil	
Original	20	15	
Number examined for tumors	20	15	
Number of mice with tumors	4	2	Benign papilloma
Number of tumors observed	4	3	Benign papilloma

[a]Source: Salamon and Roe, 1956

[b]Control - Croton oil in acetone, applied to the skin of the back once weekly. Week 1-18, 0.17% croton oil

[c]Acrolein in acetone - 10 weekly applications of 0.5% acrolein, followed by 18 weekly applications of 0.3 ml croton oil in acetone. Total acrolein dose = 12.6 mg/animal.

body weight into five groups. Two groups consisted of 18 males and 18 females each; each of the other three groups comprised 30 males and 30 females. The treatment of the hamsters in the various groups is presented in Table 5-3. Acrolein vapor was dosed at an average concentration of 4.0 ppm (9.2 mg/m^3), 7 hours/day, 5 days/week, for a period of 52 weeks.

The experiment was terminated after 81 weeks, when all survivors were killed and autopsied. Hamsters that died spontaneously or were killed when moribund were also subjected to a complete autopsy. The entire respiratory tract, grossly visible tumors, and gross lesions suspected of being tumors from all animals were examined histologically.

Exposure to acrolein vapor caused slight to moderate inflammation and epithelial metaplasia of the nasal cavity. Lesions occurred in the anterior half, mainly in the dorsomedial region and on the nasomaxillary turbinates. They consisted of neutrophilic infiltrates in the mucosa and submucosa, thickening of the submucosa due to an increased amount of fibrous tissue, reduction of the number of subepithelial glands, and metaplastic stratified squamous epithelial that occasionally showed keratinization. Neutrophilic exudation in the lumen was seen in a few animals.

About 20% of the animals killed terminally (at week 81, after a withdrawal period of about 6 months) still showed treatment-related lesions in the nasal cavity. These consisted mainly of a thickened submucosa and exudation in the lumen.

No respiratory tract tumors were found after exposure to acrolein vapor alone, except for a small tracheal papilloma in one female hamster killed in moribund condition in week 74 (Table 5-4 and 5-5). This effect not regarded as an indication of the carcinogenic activity of acrolein.

TABLE 5-3

Treatment of the Animals Exposed to either Air or Acrolein Vapor (4.0 ppm)[a]

Initial Number of Hamsters per Sex per Inhalation Chamber	Mode, Level, and Frequency of Administration
18	None
18	Weekly, it[b], 0.2 ml in 0.9% NaCl, 52 weeks
	Weekly, it[b], 0.2 ml 0.175% B(a)P in 0.9% NaCl 52 weeks[c]
30	Weekly, it[b], 0.2 ml 0.35% B(a)P in 0.9% NaCl, 53 weeks[d]
30	Once every 3 weeks, s.c. injection, 0.2 ml 0.0675% DENA in 0.9% NaCl, 52 weeks[e]

[a]Source: Feron and Kruysse, 1977

[b]Intratracheal instillation. Before each instillation the animals were lightly anesthetized with freshly distilled ether.

[c]Total amount of B(a)P instilled, 18.2 mg

[d]Total amount of B(a)P instilled, 36.4 mg

[e]Total amount of DENA injection, 2.1 μρ given 17 three times/week dose of 0.125 μρ

TABLE 5-4

Incidence and Site of Respiratory Tract Tumors in Hamsters Exposed to Air or Acrolein Vapor and Treated Intratracheally with B(a)P or Subcutaneously with DENA[a]

Treatment			Number of Animals with Tumors of						
Inhaled	Intratracheally Instilled	Effective No. of Animals	Respiratory Tract (total)	Nasal Cavity	Larynx	Trachea[b]	Bronchi	Lungs	Total No. of Respiratory Tract Tumors
MALES	B(a)P								
Air	---	15	0 (0%)	0	0	0	0	0	0
Air	0.9% NaCl	15 30							
Air	B(a)P (18.2 mg)	29	4 (14%)	0	0	2	1	2	5
Air	B(a)P (36.4 mg)	30	19 (63%)	0	1	8	3	13	27
Air	[c]	29	12 (41%)	2	7	3	3	0	15
Acrolein	---	15	0 (0%)	0	0	0	0	0	0
Acrolein	0.9% NaCl	15 30							
Acrolein	B(a)P (18.2 mg)	30	7 (23%)	0	0	3	1	3	7
Acrolein	B(a)P (36.4 mg)	29	19 (66%)	0	1	11	4	10	29
Acrolein	[c]	30	10 (33%)	1	4	6	0	0	11
FEMALES									
Air	---	14	0	0	0	0	0	0	0
Air	9.0% NaCl	14 26							
Air	B(a)P (18.2 mg)	27	3 (11%)	0	1	0	1	1	3
Air	B(a)P (36.4 mg)	24	7 (29%)	0	0	3	1	5	9
Air	[c]	27	11 (41%)	0	3	8	2	0	13
Acrolein	---	14	1 (4%)	0	0	1	0	0	1
Acrolein	0.9% NaCl	13 27							
Acrolein	B(a)P (18.2 mg)	29	8 (28%)	0	0	4	0	4	8
Acrolein	B(a)P (36.4 mg)	30	15 (50%)	0	0	8	1	13	22
Acrolein	[c]	28	11 (39%)	0	5	8	2	0	15

[a]Source: Feron and Kruysse, 1977

[b]Tumors found in the interlaryngotracheal zone are classified as laryngeal neoplasms.

[c]Subcutaneously injected with DENA

TABLE 5-5

Site, Type, and Incidence of Respiratory Tract Tumors in Hamsters Exposed To Air or Acrolein Vapor and Treated Intratracheally with B(a)P or Subcutaneously with DENA[a]

Site and Type of Tumors	Incidence of Tumors										
	Inhalation of Air						Inhalation of Acrolein				
	B	0.9% NaCl[c]	B(a)P[d] (18.2 mg)	B(a)P[e] (36.4 mg)	DENA[f]	B	0.9% NaCl[c]	B(a)P[d] (18.2 mg)	B(a)P[e] (36.4 mg)	DENA[f]
MALES										
No. of Animals examined[g]	15	30	15	29	30	29	15	30	15	30	29	30
Nasal cavity												
Polyp		0		0	0	1		0		0	0	0
papilloma		0		0	0	0		0		0	0	0
Adenocarcinoma		0		0	0	1		0		0	0	0
Larynx												
Papilloma		0		0	1	7		0		0	1	4
Trachea												
Polyp		0		0	0	2		0		1	2	1
Papilloma		0		2	5	1		0		3	3	5
Squamous cell carcinoma		0		0	1	0		0		0	3	0
Anaplastic carcinoma		0		0	1	0		0		0	2	0
Sarcoma		0		0	1	0		0		1	1	0
Bronchi												
Polyp		0		0	0	1		0		0	2	0
Papilloma		0		1	2	2		0		1	0	0
Adenoma		0		0	0	0		0		0	1	0
Adenocarcinoma		0		0	1	0		0		0	2	0
Lungs												
Papillary adenoma		0		0	6	0		0		0	4	0
Acinar adenoma		0		1	3	0		0		1	3	0
Adenosquamous adenoma		0		1	2	0		0		1	1	0
Adenocarcinoma		0		0	2	0		0		0	0	0
Adenosquamous carcinoma		0		0	0	0		0		0	1	0
Squamous cell carcinoma		0		0	1	0		0		1	1	0
Oat cell-like carcinoma		0		0	0	0		0		0	1	0
Anaplastic carcinoma		0		0	1	0		0		0	0	0

TABLE 5-5 (cont.)

Site and Type of Tumors	Incidence of Tumors: Inhalation of Air						Inhalation of Acrolein					
	0[b]	0.9% NaCl[c]	B(a)P[d] (18.2 mg)	B(a)P[e] (36.4 mg)	DENA[f]		0[b]	0.9% NaCl[c]	B(a)P[d] (18.2 mg)	B(a)P[e] (36.4 mg)	DENA[f]	
FEMALES												
No. of Animals examined	14	28	14	27	24	27	14	27	13	29	30	28
Larynx												
Papilloma		0		1	0	3		0		0	0	5
Trachea												
Polyp		0		0	0	0		0		1	0	0
Papilloma		0		0	0	8		1		3	6	8
Squamous cell carcinoma		0		0	2	0		0		0	2	0
Bronchi												
Polyp		0		0	0	0		0		0	0	1
Papilloma		0		1	0	2		0		0	0	1
Adenocarcinoma		0		0	1	0		0		0	0	0
Squamous cell carcinoma		0		0	0	0		0		0	1	0
Lungs												
Papillar adenoma		0		0	3	0		0		2	4	0
Acinar adenoma		0		0	2	0		0		2	5	0
Adenosquamous adenoma		0		1	0	0		0		0	2	0
Squamous cell carcinoma		0		0	0			0		0	1	0
Oat cell-like carcinoma		0		0	0	0		0		0	1	0

[a]Source: Feron and Kruysse, 1977

[b]No further treatment

[c]Given intratracheally (0.2 ml) weekly during 52 weeks

[d]Given intratracheally in 52 weekly doses of 0.35 mg

[e]Given intratracheally in 52 weekly doses of 0.70 mg

[f]Given subcutaneously in 17 three-weekly doses of 0.125 ml

[g]A few hamsters were lost through cannibalism or autolysis

There were no changes in other parts of the respiratory tract or outside the airway system that could be attributed to acrolein. Randomly distributed histopathological changes unrelated to treatment included: nephrosis, hepatic cysts, testicular atrophy, accumulation of reticuloendothelial cells in the liver, accumulation of macrophages in pulmonary alveoli, dilated gastric glands, myodegeneration of skeletal muscle, slight proliferation of bile dicts in the liver, amyloidosis of the liver, kidneys, and adrenals, and cystic follicles in the thyroid.

5.1.1. Respiratory Tract Tumors Following Treatment With B(a)P and Exposure to Air or Acrolein. The incidence of B(a)P-induced respiratory tract tumors in the low-dose group (18.2 mg B(a)P) was found to be slightly higher, although statistically insignificant, in animals exposed to acrolein vapor than in those exposed to air. The percentages of these tumors was found to be 14 and 11 for air-exposed male and females, respectively (see Table 5-4). In the high-dose group (36.4 mg B(a)P) females exhibited a similar difference, the percentages of females bearing tumors of the respiratory tract being 28 and 50 after air and acrolein exposure, respectively (see Table 5-4). However, in males of the high-dose group such a difference did not occur at all (63 and 66% tumor-bearers after air exposure and 66% after exposure to acrolein; see Table 5-4).

As to the time of appearance of the B(a)P dose group a marked difference appeared to exist between air- and acrolein-exposed hamsters. This difference suggested a shortening of the latent period of the neoplasms caused by acrolein vapor.

Tumors of the trachea and lungs were encountered most frequently, but bronchial and laryngeal neoplasms were seen, one a tracheal sarcoma and the other a pulmonary squamous cell carcinoma. Both tumors occurred in

acrolein-exposed animals. In the high-B(a)P-dose group, a total of 27 malignant neoplasmn were observed, 11 in animals exposed to air (8 in males and 3 in females) and 16 in acrolein-treated animals (11 in males and 5 in females).

Respiratory tract tumors were observed following treatment with DENA and exposure to air or acrolein. There were no significant difference in incidence, site, and type of DENA-induced respiratory tract tumors between hamsters exposed to air and those exposed to acrolein vapor (see Table 5-4 and 5-5). The most common type of DENA-induced tumor was papilloma of the larynx or trachea (see Table 5-5). Only one malignant tumor was found in the repiratory tract following treatment with DENA. This was a adenocarcinoma in the nasal cavity of a male exposed to air.

Tumors appeared slightly earlier in both males and females exposed to acrolein than in those exposed to air. However, the differences were insufficiently clear to consider them an indiction of a reduced latent period caused by acrolein.

5.1.2. Tumors Outside the Respiratory Tract. The following tumors were found in organs other than the respiratory tract: three light cell tumors and two papillary adenomas of the thyroid, two adrenocortical adenomas, one leukemia, one hepatocellular tumor, one thoracic sarcoma, one renal adenocarinoma, and one lymphoreticular malignancy in lymph nodes. The distribution of these neoplastic lesions over the various groups did not suggest a relationship between the tumors and any of the treatments. The author concluded that exposure to crolein resulted in abnormal behavior, growth retardation, increases in hemoglobin content, packed cell volume, and relative lung metaplasia of the epithelium in the nasal cavity. There was no indication of a carcinogenic activity of acrolein. Respiratory tract

tumors were found in males and females treated with B(a)P or DENA. The tyupes of tumors found were those usually seen in hamsters following administration of these carcinogens.

Indication of an enhancing effect of acrolein on B(a)P carcinogenesis were doubtful. The carcinogenic effect of DENA on the respiratory tract appeared not to be influenced by exposure to acrolein vapor. It was concluded that the study produced insufficient evidence to enable acrolein to be regarded as a carcinogen or cofactor in respiratory tract carcinogenesis.

Metaplastic lesions were seen only in the nose in response to acrolein exposure, indicating that nasal cells are more responsive to acrolein exposure. There was no chance for interaction with the carcinogens, B(a)P or DENA, which affect the more distal respiratory tract. In humans, a sharp localization to the nose would not be expected and there would be a better chance for interaction with carcinogens in the lung. Furthermore, the hamster is not a very sensitive model for respiratory carcinogenesis bioassay by inhalation. If the IARC criteria were used, this evidence would be judged inadequate to make any conclusions regarding the carcinogenicity of acrolein.

5.2. MUTAGENICITY

Results of mutagenicity studies of acrolein are equivocal (Table 5-6). Negative results were obtained for acrolein by Andersen et al. (1972) in tests using eight histidine requiring mutants of Salmonella typhimurium. Bignami et al. (1977) found positive mutagenic effects with S. typhimurium strains TA1538 and TA98, but obtained negative results with strains TA1535 and TA100. Florin et al. (1980), in mutagenicity assays using S. typhimurium strains TA98, TA100, TA1535 and TA1537, with and without the S-9 fraction from rat liver, found that acrolein was not mutagenic. In tests with

TABLE 5-6

Mutagenicity of Acrolein*

Assay	Indicator/Organism	Application	Concentration or Dose	Activating System	Response	Reference
Reverse mutation	Salmonella typhimurium 8 strains	plate incorporation	1-5 µl of "liquid preparation"	±S-9	negative	Anderson et.al., 1972
	TA98	spot test	0.3 µmol/plate	±S-9	negative	Florin et al., 1980
	TA100	plate incorporation	0.005-1 µmol/plate	±S-9	negative	Loquet et al., 1981
	TA100	plate incorporation	NR	±S-9	negative	Bignami et al., 1977
	TA1537	spot test	0.3 µmol/plate	±S-9	negative	Florin et al., 1980
	TA1535	spot test	0.3 µmol/plate	±S-9	negative	Florin et al., 1980
	TA1535	plate incorporation	0.001-1 µg/plate	±S-9	negative	Hales, 1983
	TA1535	plate incorporation	NR	±S-9	negative	Bignami et al., 1977
	TA1535	plate incorporation	NR	±S-9	positive	Lijinsky and Andrews, 1980
	TA100	plate incorporation	0-0.15 µmole/plate	+S-9	negative	Lutz et al., 1982
	TA100	plate incorporation	NR	-S-9	positive	Eder et al., 1982
	TA1538	plate incorporation	NR	±S-9	positive	Bignami et al., 1977
	TA1535	plate incorporation	0-100 µg/plate	±S-9	positive	Haworth et al., 1983

TABLE 5-6 (Cont.)

Assay	Indicator/Organism	Application	Concentration or Dose	Activating System	Response	Reference
Reverse mutation	TA1537 TA98 TA100	plate incorporation	0-100µg/plate	±S-9	positive positive positive	Haworth et al., 1983
Reverse mutation	TA98 TA1528	plate incorporation	NR	±S-9	positive	Bignami et al. 1977
Reverse mutation	S. typhimurium D3052	plate incorporation	0-200 µmol/plate	±S-9	negative	Basu and Marnett, 1984
Reverse mutation	Escherishia coli K-12/343/113	plate incorporation	NR	mouse ±S-9	negative	Ellenberger and Mohn, 1976, 1977
	WPµvrA	plate incorporation	20-10,000 µM	none	weakly positive	Hemminki et al., 1980
	DNA polymerese deficient	plate incorporation	NR	none	positive	Billmoria, 1975
Reverse mutation	Saccharomyces cerevisiae M123 S211 S138	plate incorporation	160-640 mg/l	none	negative negative negative	Izard, 1973
Chromosomal aberration	MB1072-2B	plate incorporation	10^{-4}M	none	negative	Fleer and Brendel, 1982
Recessive lethal	Drosophila melanogaster	treatment of larva	NR	none	positive 15 mutations in 671 chromosomes	Rapoport, 1948
Cell multipli-cation	Dunaliella bioculata		$1x10^{-4}$M	none	inhibition of division	Izard, 1967
	S-180 cell culture	mixed in culture	$2.6-3.5x10^{-5}$ µmol/ml	none	inhibition of division	Alarcon, 1964

TABLE 5-6 (Cont.)

Assay	Indicator/Organism	Application	Concentration or Dose	Activating System	Response	Reference
DNA,RNA synthesis	polyoma transformed Chinese hamster cell lines	added to culture	0.8-2.5x10^{-5} for one hour	none	inhibition	Alarcon, 1972
	mouse kidney monolayer	cell culture	70 µg	none	inhibition	Leuchtenberger et al., 1968
DNA,RNA synthesis	rat liver cell nuclei	in vitro	NR	none	inhibition	Moule and Frayssinet, 1971
	rat liver and rat lung in vivo	injected	50-270 µg/100 g	NA	inhibition	Munsch and Frayssinet, 1971
	Escherichia coli	plate incorporation	NR	none	inhibition	Kimes and Morris, 1971
Activity of DNA polymerese	rat liver	plate incorporation	NR	none	inhibition	Munsch et al., 1973, 1974
	Escherichia coli		NR	none	stimulation	Munsch et al., 1973, 1974
Chromosome breakage and sister chromatid exchange	Chinese hamster ovary cell	added to culture	0-40 µM	±S-9	positive	Au et al., 1980
Unscheduled DNA synthesis	HeLa cells	added to culture	5x10^{-6}-10^{-3} mol/l	none	undetermined*	Schiffman et al., 1983
Mutagenicity	ICR/Ha Swiss mice	intraperitoneal injection	1.5 and 2.2 mg/kg	none	negative	Epstein et al., 1972

*Concentrations were toxic to cell

NR = Not reported; NA = not applicable

S. typhimurium strains TA98 and TA100 with and without rat liver S-9, acrolein also did not produce a mutagenic response (Loquet et al., 1981). Hales (1983) found that acrolein was not mutagenic in the absence of liver microsomes, but was weakly mutagenic in the presence of liver microsomes with S. typhimurium strain TA1535. Conversely, Lijinsky and Andrews (1980) found acrolein to be mutagenic when tested with S. typhimurium TA1535. Using S. typhimurium strain TA100, Lutz et al. (1982) reported that acrolein exhibited a direct mutagenic response three times higher than allyl alcohol (750 revertants/μmole) in tests without S-9 and no revertants in the presence of S-9.

Haworth et al. (1983), using the Salmonella/mammalian microsome test with strains TA1535, TA1537, TA98 and TA100 with and without S-9, and a dose range of 0-100 μg/plate found a positive response with acrolein.

Basu and Marnett (1984) found that acrolein was not mutagenic with S. typhimurium strain his D3052, but that β-substituted derivatives were mutagenic. . These authors found that a good leaving group at the β position increased mutagenic activity and that nucleophilic attack at the β substituent is important for mutagenicity; however, substitution of a methyl group at the α-carbon abolished the mutagenicity of these compounds. The presence of S-9 has no effect on mutagenicity. The β-substituted acroleins were not mutagenic in strains TA98 and TA100; however, the parent compound, acrolein, was mutagenic in TA100 (Eder et al., 1982).

Izard (1967) inhibited the multiplication of the unicellular marine alga Dunaliella bioculata, with a dosage of 1 mg/ℓ of acrolein. Binding of ^{3}H-acrolein to occurred with nucleic acids of Dunaliella, remaining stable for ≥2 days (Marano, 1976; Marano and Demestere, 1976). Incorporation of ^{3}H-uridine, ^{3}H-thymidine, and ^{3}H-leucine was inhibited by acrolein

applied to polyoma-transformed Chinese hamster cell lines (Alarcon, 1972). Inhibition of RNA synthesis was observed in primary cultures of mouse kidney tissue, as monitored by a progressive decrease in the uptake of ^{3}H-uridine (Leuchtenberger et al., 1968). When acrolein was added to preparations of isolated rat liver cell nuclei, inhibition of RNA transcription was observed for nuclear and nucleolar RNA (Moule and Frayssinet, 1971). Munsch and Frayssinet (1971) observed inhibition of DNA synthesis proportional to dose in the lungs of rats injected with 50-270 µg of acrolein per 100 g body weight. Munsch et al. (1973,1974) observed inhibition of rat liver DNA polymerase by acrolein , but in Escherichia coli DNA polymerase was activated by acrolein. Binding of ^{3}H-acrolein to DNA in the rat liver system was irreversible.

Au et al. (1980) tested acrolein for chromosome breakage and changes in the mitotic index in a Chinese hamster ovary cell line. Acrolein was so toxic in the dose range of 10-100 µM that the mitotic rate was <1 in 2000 cells; the presence of S-9 had little effect. Acrolein induced a dose-dependent increase in sister chromatid exchange in the absence of S9 in doses ranging from 0-10 µM with breakage occurring above these levels. The presence of S-9 alleviated this effect.

No measurement of unscheduled DNA synthesis in HeLa cells was possible at acrolein concentrations of $5x10^{-3}$-10^{-3} mol/ℓ because of its toxicity (Schiffmann et al., 1983).

Acrolein exhibited no mutagenic activity in E. coli K-12/343/113 in the presence or absence of mouse liver S-9 (Ellenberger and Mohn, 1976, 1977), but in an E. coli strain deficient in DNA polymerase, acrolein was mutagenic (Bilimoria, 1975). In tests with E. coli strain WP2uvrA, in a dose range of 20-10,000 µM for acrolein, without metabolic activation, acrolein was

weakly mutagenic (Hemminki et al., 1980). Acrolein induced no cytoplasmic respiration deficiency in Saccharomyces cerevisiae N123 and was also negative for reverse-mutation with strains S211 and S138 (Izard, 1973). Using S. cerevisiae, acrolein did not induce interstrand cross-links and DNA fragmentation in an in vitro test system that detects <1 cross-link per chromosome (Fleer and Brendel, 1982).

Rapoport (1948) found that acrolein induced an increased rate of recessive lethal mutations in Drosophila melanogaster. Epstein et al. (1972) investigated mutagenicity with a dominant-lethal assay in IRC/Ha Swiss mice. At doses of 1.5 and 2.2 mg/kg injected intraperitoneally to male mice before mating, no effect on early fetal death or preimplantation loss was observed.

5.3. TERATOGENICITY

Hales (1982) administered acrolein by injection into the amniotic fluid of embryos on day 13 of gestation following laparotomy of pregnant Sprague-Dawley rats. Embryos in one uterine horn received either an injection of 10 µl of 0.9% sodium chloride or 10 µl of 0.9% sodium chloride containing acrolein. After injection, the uterus was replaced and the laparotomy was sutured. Dams were killed on day 20 of gestation. Doses of 100 µg (1.8 µmol/fetus) and 10 µg (0.18 µmol/fetus) killed 98 and 100% of the injected fetuses, respectively. Injection of 1 µg (0.018 µmol/fetus) induced malformations in 85.7% of the live fetuses. Malformations included edema (7%), hydrocephaly (43%), open eyes (7%), cleft palate (7%), enphalocele (29%); forelimb (50%), hindlimb (50%), and tail (21%) defects. A dose of 0.1 µg (0.002 µmole/fetus) had no greater effect on resorption or malformation than injection of saline in controls.

Claussen et al. (1980) injected rabbit embryos in the yolk sac with 0.84% acrolein in physiological saline in doses of 10 µl; 20 µl; and

40 µl per blastoderm, on the 9th day of gestation. Malformations increased in a dose-related manner and included deformed and asymmetric vertebrae, spina bifida aperta, deformed and accreted ribs and lack of and fusion of sternum segments. Malformations also occurred in surviving embryos after injection of the dams intravenously with 3 mg/kg, 4.5 mg/kg and 6 mg/kg of acrolein on the 9th day of gestation. Deformed and asymmetric vertebrae, spina bifida aperta, deformed and accreted ribs, lack and fusion of sternum segments and microphthalmia were observed. Incidences are summarized in Table 5-7.

Schmid et al. (1981) examined the effect of cyclophosphamide on the development of 10.5-day rat conceptuses in vitro, cultured in the presence of liver microsomes and NADPH. Development was retarded, and stunted telencephalic regions, hypoplasia of the mandibular bars, hypoplasia of the forelimb buds and short trunks were observed. In the absence of liver microsomes and NADPH, the developmental aberrations did not occur. Treatment of the embryos with acrolein did not induce malformations, but growth was markedly inhibited. Schmid et al. (1981) concluded that acrolein was fetotoxic, but was not responsible for the teratogenic effect of cyclophosphamide.

Stahlmann et al. (1981) studied the teratogenicity of acrolein in vitro using mouse limb buds in a medium free of -SH compounds. At concentrations of 1 µg/ml acrolein in the culture medium, no effect was observed. At 10 µg/ml, paws were bent at the wrist forming a 90° angle. At 30 µg/ml, only the metacarpalia developed, but all of the phalanges were missing. Differentiation of the paw skeleton was completely inhibited at 100 µg/ml, but development of the "long bones" was still discernable.

TABLE 5-7

Malformations and Retardations After Intravenous Injection of Acrolein to Rabbits on the 9th Day of Gestation*

Malformation	Saline	Acrolein in Saline		
		3 mg/kg	4.5 mg/kg	6 mg/kg
Vertebral column	2/121	4/133	7/77	5/69
Sternum	3/121	9/133	2/77	2/69
Vertebral column and sternum	4/121	3/133	0/77	5/69
Vertebral and rib	0/121	0/133	1/77	0/69
Sternum and rib	0/121	1/133	0/77	0/69
Spina bifida	0/121	0/133	0/77	1/69
Vertebral, sternum, rib	0/121	1/133	0/77	0/69
Vertebral, sternum, rib, head	0/121	0/133	0/77	1/69
Total malformations	9/121 (7%)	18/133 (14%)	10/77 (13%)	14/69 (20%)

*Source: Claussen et al., 1980

Mirkes et al. (1981) compared the effects of the major metabolites of cyclophosphamide (4-ketocyclophosphamide, phosphoramide mustard, and acrolein) on Sprague-Dawley rat embryos (day 10 of gestation) cultured for 24 hours. Acrolein at a dose of 5 µg/mℓ produced no malformed embryos and no statistically significant effect on protein content, somite number, or crown-rump length. Embryo viability was 89%, however, with a dose of 10 µg/mℓ, all the embryos died. It was suggested that phosphoramide mustard was the active teratogenic agent. A synergistic effect was observed in embryos exposed to phosphoramide mustard and acrolein, perhaps because phosphoramide had a cytotoxic effect on the yolk sac, which diminished the yolk sac barrier to acrolein.

In another study, Mirkes et al. (1984) used the decloro-derivative of cyclophosphamide, which spontaneously decomposes to acrolein and dechlorophosphoramide mustard, a nonalkylating derivative of phosphoramide mustard. Dechlorophosphoramide mustard, even at concentrations of 238 µg/mℓ, had no effect on the growth and development of day 20 rat embryos (Sprague-Dawley). Dechlorocyclophosphamide in concentrations ranging from 6.25-50 µg/mℓ produced concentration-dependent cell death, growth retardation and malformations. Exposure of embryos to acrolein in doses of 0.025-0.1 µg/mℓ produced concentration-dependent decreases in growth parameters and abnormal flexion in some embryos. Data are presented in Table 5-8. At all concentrations of acrolein tested, some embryos were abnormal (abnormal flexion) but the abnormalities were not similar to those observed in cyclophosphamide or dechlorocyclophosphamide-treated embryos.

Spielmann and Jacob-Mueller (1981) conducted experiments in cultured preimplantation mouse embryos <u>in vitro</u> in the four-cell and eight-cell stage to the blastocyst stage. Acrolein inhibited blastulation in a dose-dependant manner in concentratons of 1 µM, 10 µM and 100 nM and

TABLE 5-8

Effects of Acrolein on Growth and Development of Day 10 Rat Embryos *In Vitro*[a,b]

Dose (µg/mℓ)	No. of Embryos Exposed	Crown-rump Length (mm)	No. of Somites	Protein Content (µg/embryo)	Percentage Viable	Percentage Malformed[c]
0.005	18	2.8±0.3 (17)	20.5±1.3 (17)	224±40 (17)	94	24
0.025	16	2.7±0.3 (16)	20.3±1.4 (16)	212±59 (16)	94	20
0.05	25	2.6±0.3[d] (21)	18.8±4.7[d] (21)	186±65[d] (21)	84	38
0.075	12	2.5±0.3[d] (11)	18.8±1.7[d] (11)	165±36[d] (11)	92	55
0.10	15	2.6±0.2[d] (8)	19.1±1.4[d] (8)	184±41[d] (8)	53	38
0.50	16	NA	NA	NA	0	NA
5.0	18	NA	NA	NA	0	NA

TABLE 5-8 Cont)

Dose (µg/mL)	No. of Embryos Exposed	Crown-rump Length (mm)	No. of Somites	Protein Content (µg/embryo)	Percentage Viable	Percentage Malformed[c]
HBSS control[e]	30	2.8±0.2 (29)	20.4±1.2 (29)	219±48 (29)	97	3[f]
Serum control	13	2.8±0.3 (10)	20.2±1.4 (10)	208±37 (10)	77	0

[a]Source: Mirkes et al., 1984

[b]Embryos were exposed to acrolein for 2 hours in Hank's balanced salt solution (HBSS) at 37°C with rotation, transferred to culture medium, and incubated for an additional 22-24 hours. Values are means ±standard deviation. Numbers in parentheses indicate number of viable embryos.

[c]Acrolein-induced malformations consisted of embryos with abnormal flexion.

[d]Values are significantly different from HBSS or serum control values at $p<0.05$.

[e]Embryos were incubated in HBSS for 2 hours at 37°C with rotation, transferred to culture medium, and incubated for an additional 22-24 hours.

[f]One embryo exhibited hypoplastic mesencephalon.

NA = Not applicable.

4-hydroxycyclophospamide caused inhibition at concentrations 100 times lower than acrolein. In summary intravenous injection of ≥3 mg/kg acrolein to pregnant rabbits on gestational day 9 resulted in dose-related increased incidences of fetal deaths and malformations (Claussen et al., 1980). Retarded growth, malformations and death of embryos were also observed in studies in which explanted animal embryos were cultured with acrolein in vitro or acrolein was injected intrauterinely directly into the amniotic fluid or yolk sac (Hales, 1982; Claussen et al., 1980; Schmid et al., 1981; Stahlmann et al., 1981; Mirkes et al., 1981; Spielmann and Jacob-Mueller, 1981). It should be noted that experiments performed in vitro or by direct injection into the uterus may not reflect the response obtained following administration by national route.

5.4. OTHER REPRODUCTIVE EFFECTS

In postimplantation embryos, in vitro acrolein was embryolethal but not teratogenic (Schmid et al., 1981). Acrolein was added to culture medium containing rat conceptuses explanted from the uterus on day 10.5 of gestation. Slight but statistically significant growth inhibition was observed at concentrations of 100 μM and 150 μM. Concentrations of 200 μM and 250 μM resulted in drastic inhibition of growth and differentiation, but no gross structural defects were observed.

Embryotoxicity in rabbits was observed by Claussen et al. (1980) using acrolein doses of 3, 4.5 and 6 mg/kg administered intravenously to pregnant females on the 9th day of gestation. Lethality occurred in a dose-related manner and also affected the dams; 3/16 injected with 4.5 mg/kg and 6/16 injected with 6 mg/kg died the following day. Increased resorption of fetuses was observed at 6 mg/kg ($p=0.01$). Epstein et al. (1972) observed no differences in the number of early fetal deaths and preimplantation losses

in mutagenicity studies using ICH/H Swiss mice injected intraperitoneally at dosage levels of 1.5 and 2.2 mg/kg.

5.5. CHRONIC TOXICITY

Albin (1962) exposed rats to acrolein at concentrations of up to 200 mg/ℓ for 90 days in drinking water. A slight weight reduction was observed at the highest level tested, which was attributed to dislike of the drinking water by the rats.

As reviewed by NAS (1977), Newell (1958) reported similar results. In one study, acrolein was added to drinking water in concentrations of 5, 13, 32, 80 and 200 mg/ℓ and administered to rats for 90 days. No effects on hematologic parameters, organ weight or pathology were observed. The only effect noted was decreased water consumption during the first 3 weeks of the experiment. In another experiment, male rats were given 600, 1200 and 1800 mg/ℓ of acrolein in their drinking water for 60 days. All animals died from lack of water intake at the 1200 and 1800 mg/ℓ level, and 1/5 animals died at the 600 mg/ℓ concentration. No other effects were observed.

In an inhalation study, Bouley et al. (1975,1976) exposed rats continuously to 1.26 mg/m³ of acrolein for up to 77 days. Respiratory disorders and respiratory tract irritation were evident during the first 3 weeks of exposure. Even though the effects persisted after the initial 3 weeks, adaptation to these levels of acrolein occurred, with respiratory disorders disappearing. Decreased numbers of alveolar macrophages with increased susceptiblity to respiratory infection were the major effects during this early period of exposure. Prolonged exposure resulted in lowered food consumption and decreased weight gain. During the initial 3-week exposure, a transitory hepatic effect was also noted , with decreased liver weight and increased serum acid phosphatase levels; however, these effects disappeared

with prolonged exposure. In an earlier study, Bouley (1973) exposed rats by inhalation to 1.2 mg/m³ for 1 month and noted decreased growth rate and decreased levels of oxidation-reduction coenzymes in the liver. The only significant effect in all of the above experiments was a lower mean body weight compared with controls, which lasted as long as the animals were exposed.

ALthough Philippin et al. (1969) observed a significant decrease ($p<0.01$) in body weight in mice exposed by inhalation to 13.8 mg/m³ and 34.5 mg/m³ acrolein for 6 hours/day, 5 days/week for 6 weeks, the decrease was not dose-related or very large (~6%).

Rats, guinea pigs, monkeys and dogs were exposed by inhalation to 1.6 mg/m³ (0.7 ppm) and 8.5 mg/m³ (3.7 ppm) for 8 hours/day, 5 days/week for 6 weeks or continuously to 0.48, 0.53, 2.3 and 4.1 mg/m³ for a total of 90 days (Lyon et al., 1970). Animals were observed for signs of toxicity, mortality, change in weight and hematological, biochemical, pathological and histopathological parameters. In dogs and monkeys exposed repeatedly to 8.5 mg/m³, squamous metaplasia and basal cell hyperplasia of the trachea occurred, along with necrotizing bronchitis and bronchiolitis. Squamous metaplasia in the lungs was observed in 7/9 monkeys. Similar pathology was noted in rats, dogs and monkeys continuously exposed to 2.3 and 4.1 mg/m³ acrolein. In addition, dogs and monkeys displayed signs of eye irritation, and rats had decreased weight gain.All animals repeatedly exposed to 1.6 mg/m³ of acrolein developed chronic lung inflammatory changes, which were more pronounced in dogs and monkeys than in rats and guinea pigs (Lyon et al., 1970).

Both male and female rats exhibited significantly lower ($p<0.005$) body weight with repeated exposure to 8.5 mg/m³ and continuous exposure at 2.3

and 4.1 mg/m³ of acrolein. Body weight was not affected in guinea pigs, dogs and monkeys. Rats exposed continuously to 0.48-0.53 mg/m³ exhibited no significant histopathological aberrations and gained weight normally. Histopathological examination at this concentration showed no effects in rats and guinea pigs, but dogs and monkeys exhibited inflammatory changes. At the 2.3 mg/m³, concentration dogs showed focal inflammatory reactions in the lung, liver and kidneys; guinea pigs showed pulmonary inflammation; and both rats and guinea pigs had focal liver necrosis (Lyon et al., 1970).

Another multi-species study was performed by Feron et al. (1978), who exposed hamsters (20), rats (12) and rabbits (4) to inhalation concentrations of 0.92, 3.2 and 11 3 mg/m³ for 6 hours/day, 5 days/week for 13 weeks. At 11.3 mg/m³, all animals showed signs of eye irritation and decreased food consumption and weight gain. Histopathological changes in the respiratory tract included destruction, hyperplasia and metaplasia of the epithelial lining and inflammatory alterations. Female hamsters had statistically significant increases in erythrocyte number, packed cell volume, hematocrit and lymphocyte number and decreased numbers of neutrophils. Organ weight changes included increased relative lung weight in all species, increased heart and kidney weight in hamsters and rats, and increased adrenal weight in rats. Other findings were negative in hamsters and rabbits.

At the 3.2 mg/m³ level, decreased body weight gain was observed in rats and rabbits but not in hamsters. Squamous metaplasia and neutrophilic infiltration of the mucosa of the nasal cavity occurred in rats but not in hamsters. No remarkable changes were observed at the lowest concentration,

0.92 mg/m³, in hamsters and rabbits but rats displayed slight treatment-related changes such as depression of growth, minimal histopathological changes in the nasal cavity and slight decreases in kidney and testicular weights. Effects observed in this study are summarized in Table 5-9.

In another study, Feron and Kruysse (1977) exposed hamsters to long-term inhalation of acrolein. Males (252) and females (252) were exposed to 9.2 mg/m³ of acrolein for 7 hours/day, 5 days/week for 52 weeks. At the end of the 52-week treatment period, six experimental and six control animals of each sex were sacrificed. The other hamsters were used for intratracheal instillation of benzo[a]pyrene or s.c. injection of diethylnitrosamine or 0.9% NaCl; exposure to acrolein was discontinued, and the hamsters were observed for an additional 29 weeks. Exposure to acrolein caused growth retardation, increases in hemoglobin content, packed cell volume and relative lung weight (significant for females only); decreased relative liver weight (significant for females only) and rhinitis accompanied by hyperplasia and metaplasia of the nasal cavity epithelium. At week 81, 20% of the animals showed treatment related lesions of the nasal cavity. Similar results in hamsters were observed in a 13-week, repeated exposure study (highest level 11.24 mg/m³), except that the decrease in liver weight was not observed (Kruysse et al., 1974). The morphological effects of acrolein on the respiratory tract are further supported by other short-term inhalation experiments in several animal species (Catilina et al., 1970; Dahlgren et al., 1972; Pattle et al., 1957; Skog, 1950; Salem and Collumbine, 1960; Philippin et al., 1969).

Watanabe and Aviado (1974) demonstrated a reduction in pulmonary compliance in mice exposed by repeated inhalation to 100 mg/m³ acrolein for 30 minutes, twice a day for 5 weeks. Dahl-selected rat lines,

TABLE 5-9

Summary of Treatment-Related Effects in Hamsters, Rats and Rabbits Repeatedly Exposed to Acrolein Vapors for 13 Weeks[a] (ppm)

Parameter Affected	Effects[b]								
	Hamsters Acrolein			Rats Acrolein			Rabbits Acrolein		
	0.4	1.4	4.9	0.4	1.4	4.9	0.4	1.4	4.9
Signs of Toxicity	0	X	XXX	0	X	XX	0	X	XXX
Mortality	0	0	0	0	0	+++	0	0	0
Growth	0	0	--	-	--	---	0	-	--
Food intake	NE	NE	NE	0	-	--	0	-	--
Haematology	0	0	X	0	0	0	0	0	0
Urinary amorphous material	0	0	+	0	0	+	0	0	+
Urinary crystals	0	0	-	0	0	-	0	0	0
Organ weights									
Lungs	0	0	++	0	0	++	0	0	++
Heart	0	0	+	0	0	+	0	0	0
Kidneys	0	0	+	0	0	+	0	0	0
Adrenals	0	0	0	0	0	+++	0	0	0
Gross pathology									
Lungs	0	0	0	0	0	X	0	0	0

TABLE 5-9 Cont.)

Criteria Affected	Effects[b]								
	Hamsters Acrolein			Rats Acrolein			Rabbits Acrolein		
	0.4	1.4	4.9	0.4	1.4	4.9	0.4	1.4	4.9
Histopathology									
Nasal cavity	0	X	XXX	X	XX	XXX	0	0	XX
Larynx	0	0	X	0	0	XX	NE	NE	NE
Trachea	0	0	XX	0	0	XXX	0	0	X
Bronchi and Lungs	0	0	0	0	0	XXX	0	0	XX

[a]Source: Feron et al., 1978

[b]0 = not affected; X = slightly affected; XX = moderately affected;

XXX = severely affected; + = slightly increased; ++ = moderately increased;

+++ = markedly increased; - = slightly decreased; -- = moderately decreased;

--- = markedly decreased; NE = not examined

one susceptible to salt-induced hypertension and the other resistant, were exposed to 0.92, 3.2 and 9.2 mg/m³ acrolein for 6 hours/day, 5 days/week for 62 days by Kutzman et al. (1984). No dose-related blood pressure changes or behavioral alterations were evident in either strain of rats. At the 9.2 mg/m³ level, a marked difference in pulmonary pathology was observed between the two strains. Pulmonary edema and proliferation of lung connective tissue, along with airway epithelial necrosis and hemorrhage, were observed in the susceptible rats. The resistant rats exhibited only proliferative changes in the lung, with multifocal interstitial pneumonitis present in 4/6 rats. All susceptible rats exposed to 9.2 mg/m³ acrolein died by the 11th exposure day, while only 4/10 of the resistant rats died during the 62-day exposure period. The surviving resistant rats lost 15% of their starting weight in the first 3 weeks of the study, but subsequently regained the weight. The resistant rats had increased relative weights of lung, heart, liver and brain compared with controls. During the last week of exposure a significant gain in body weight also occurred. A 71% increase in serum alkaline phosphatase was noted in resistant rats.

At the 0.92 and 3.2 mg/m³ exposure levels, both strains of rats displayed epithelial hyperplasia or clusters of macrophages near terminal bronchiolar areas in the respiratory system. An inflammatory response with increased numbers of macrophages was found in the lungs of both strains of rat at these exposure levels.

In conclusion, it appears that rabbits, mice and hamsters are the least sensitive to inhaled acrolein, rats are the next sensitive and monkeys and dogs are the most sensitive.

5.6. OTHER RELEVANT INFORMATION

The irritant effects of acrolein on humans have been observed by a number of authors (Albin, 1962; Reist and Rex, 1977; Pattle and Cullumbine, 1956; Sim and Pattle, 1957; Prentiss, 1937; Fassett, 1962). Acrolein vapor has been used as a war gas, with levels above 2.5 mg/m³ (1 ppm) being unbearable. Severe eye and respiratory irritation occur with exposure; lachrymation and marked eye, nose and throat irritation occur within a period of 5 minutes.

Higher concentrations cause deep lung injury, and respiratory insufficiency may persist for 18 months after exposure (Champeix and Catilina, 1967). In humans a concentration of 350 mg/m³ (150 ppm) is lethal within 10 minutes (Prentiss, 1937; Brabec, 1982). Henderson and Haggard (1943) reported that exposure to 23 mg/m³ for a short time is lethal. Acrolein is involved in the irritant effect of cigarette smoke (Weber-Tschopp et al., 1976a,b, 1977) and smog (Altshuller, 1978; Schuck and Renzetti, 1960). Acrolein has been shown to cause irritant dermatitis in studies done by Lacroix et al. (1976). At a concentration of 1% in alcohol 6/48 persons showed a positive response and at 10%, 8/8 subjects had a positive response. Polymorphonuclear infiltration, papillary edema and epidermal necrosis were observed histologically when biopsies were studied. Administered either by the oral or parenteral route cyclophospamide is used as an antineoplastic agent, in the treatment of Hodgkin's disease and other lymphomas. It is also used in treatment of a variety of leukemias, multiple myeloma, mycasia fungoides, neuroblastoma, adenocarcinoma of the ovary, breast carcinoma, malignant lung neoplasma, retinoblastoma, and for transplantation procedures since it is a potent immunosuppressive agent. The

usual dose range is 10-15 mg/kg bw three times per week intravenously and orally the dose is 1-5 mg/kg bw per day. (IARC, 1981).

One of the metabolites of cyclophospamide is acrolein, which is responsible for the marked necrosis of the bladder, and renal tubular and renal pelvic epithelium seen in experimental animals given cyclophosphamide and in humans undergoing cyclophosphamide therapy. (IARC, 1981; Brock et al., 1981; Sladek et al., 1982.). After production of acrolein from liver metabolism of cyclophosphamide, especially with prolonged ingestion of the drug, hemorrahagic cystitis occurs. Acrolein accumulates in the urine after glomerular filtration of the hydroxylated metabolites. The urine contains no proteins, so the effects of acrolein are not blocked. Acrolein reacts with bladder and urinary tract proteins found in renal and vescical epithelia (Brock et al., 1979a; Wildenauer and Oehlmann, 1982). Patients undergoing cyclophosphamide therapy are given -SH group containing agents to help block the urotoxic effects from metabolic activation by liver mixed function oxidases (located in the hepatocytes) (IARC, 1979; Colvin, 1978; IARC, 1981). Examples of these agents that block the effect of acrolein are 2-mercaptoethane sodium sulphonate (Brock et al., 1979a,b; Brock, 1980); N-acetylcysteine (Berrigan et al., 1980); propylthiouracil (Chijiiwa et al., 1983); and cysteine, which prevents reaction of acrolein with glutathione in vivo (Gurtoo et al., 1981).

The other major metabolite, phosphoramide, is responsible for the carcinogenic, mutagenic, and teratogenic effects of cyclophosphamide (IARC, 1981).

With acute exposure acrolein produces severe eye and respiratory irritation (Prentiss, 1937). Animals exposed to acrolein succumb to pulmonary edema and survivors are susceptible to bronchopneumonia (Skog, 1950). Acute toxicity values for acrolein are summarized in Table 5-10.

Lung changes include edema, hyperemia, hemorrhages and degenerative changes in rats, mice, guinea pigs and rabbits (U.S. EPA, 1980). Pathological changes in liver and kidney have been observed with lethal subcutaneous doses to rats (Skog, 1950). Investigators that have described toxic effects in mammals are Boyland (1940); Carl et al. (1939); Carpenter et al. (1949); Skog, (1950); Smyth et al. (1951); Pattle and Cullumbine (1956); Phillippin et al. (1969); Salem and Cullumbine (1960). The effect of acrolein on liver enzymes has been linked to stimulations of pituitary-adrenal systems resulting in increased secretion of glucocorticoids and increased liver enzyme synthesis (Murphy et al., 1963; Murphy, 1965; Murphy and Porter, 1966). Murphy et al. (1954) reported increased liver-to-body weight ratios in rats exposed continuously by inhalation to 9.2 mg/m³ acrolein for 20 hours, but the ratios decreased after exposure to 8.9 mg/m³, 4 hours/day for 9 days. Grundfest et al. (1982), using rat lung macrophage cultures incubated in Hank's balanced salt solution, treated the cultures with 15 μM acrolein. Dose-dependent synthesis and release of thromboxane A_2 and prostaglandin E_2 was observed; the release occurred only at doses >7.5 μM. Levels of thromboxane B_2 were affected and phagocytosis was inhibited. It was suggested that the enzyme prostaglandin endoperoxide E isomerase, necessary for the conversion of endoperoxide to prostaglandin E_2, was selectively inhibited by acrolein. Leffingwell and Low (1979) found that amino acid incorporation by rabbit pulmonary alveolar macrophages exposed to 5.5 μg acrolein/mL was inhibited.

Patel et al. (1984a) gave adult male Holtzman rats i.p. doses of 5 mg/kg acrolein for 1-3 days. Significant reductions in lung mixed function oxidase activity and significant increases in glutathione content occurred along with microsomal lipid peroxide formation after 3 days of treatment.

TABLE 5-10

Oral, Inhalation and Dermal LD_{50} or LC_{50} Values for Acrolein

Route	Species	Dose Concentration	Reference
Oral	rat	46 mg/kg	ITII, 1975
Oral	mouse	28 mg/kg	Safe Drinking Water Committee, 1977
Oral	rabbit	7 mg/kg	ITII, 1975
Inhalation	rat	18 mg/m³ (8 ppm) for 4 hours	Albin, 1962
Inhalation	rat	300 mg/m³ (130 ppm) for 30 minutes	Skog, 1950
Inhalation	rat	300 mg/m³ (130 ppm) for 30 minutes	Fassett, 1963
Inhalation	dog	344 mg/m³ (150 ppm) for 30 minutes	Albin, 1962
Inhalation	mouse	2007 mg/m³ (875 ppm) for 1 minute	Albin, 1962
Inhalation	mouse	401 mg/m³ (175 ppm) for 10 minutes	Albin, 1962
Inhalation	hamster	58.4 mg/m³ (25.4 ppm) for 4 hours	Kruysse, 1971
Dermal	rabbit	200 mg/kg	Albin, 1962

In a second study, Patel et al. (1984b) found that addition of acrolein to rat lung or liver microsomal suspensions resulted in total inactivation of NADPH-cytochrome C reductase and partial conversion of cytochrome P-450 to cytochrome P-420 in a concentration- and time-dependent fashion. A total loss of nonprotein sulfhydryl content was observed in both preparations and protein sulfhydryl content was decreased by 40% in lung and 28% in liver preparations. Addition of glutathione or dithiothreitol was protective and inhibited conversion of cytochrome P-450 or inactivation of NADPH-cytochrome C reductase.

Voisin et al. (1983) found that acrolein had a cytotoxic index of 47.5% (ratio of ATP damage compared with control cells) when supplied in the gas phase to guinea pig alveolar macrophages in vitro.

Kilburn and McKenzie (1978) exposed hamsters to 13.8 mg/m³ acrolein for 4 hours and observed airway cell cytotoxicity, with both immediate and delayed exfoliation and leukocyte recruitment. Carson et al. (1966) observed reduced mucus flow rates in cats after short-term inhalation of acrolein. Inhibition of ciliary function from cigarette smoke components which include acrolein has been observed in cats (Dalhamn, 1972) and in chickens (Battista and Kensler, 1970). Cardiovascular effects of acrolein have been observed in rats (Egle and Hudgins, 1974; Basu et al., 1971), the major effect being bradycardia. An exaggerated pressor response was observed in hypertensive rats exposed to acrolein and the antihypertensive drug, guanethidine (Green and Egle, 1983). The cytotoxic effects of acrolein have been investigated by a number of authors. Alarcon (1964) found that a concentration of $2.6\text{-}3.5 \times 10^{-5}$ acrolein caused 50% inhibition in 5-180 cell cultures and Koerker et al. (1976) found acrolein to be cytotoxic to cultured neuroblastoma cells at dosages of $3.0 \times 10^{-5}\text{-}1.0 \times 10^{-6}$ M. Acrolein was also cytotoxic to Ehrlich Landschutz

diploid ascites tumor cells, causing 94% inhibition at a concentration of 100 μM (Holmberg and Malmfors 1974); however, acrolein was marginally cytotoxic (LC_{90} of 8.75 μM) to Walker 256 ascites cells that were exposed to acrolein *in vitro* for 1 hour and subsequently injected into host rats (Sladek, 1973). Similar results were obtained by Phillips (1974) using an *in vitro* test system. The 72-hour IC_{50} for acrolein was 1.0 μg/ml (18 μM). Lelieveld and Van Putten (1976) found that acrolein was inactive against normal mouse hematopoietic stem cells and osteosarcoma cells, and less active than cyclophosphamide against leukemia cells. Brock (1976) also found that acrolein is less active than cyclophosphamide against Yoshida ascitic sarcoma of the rat.

Bridges et al. (1977), in studies with human polymorphonuclear leukocytes (PMNs), found that acrolein (160 μM) was inhibitory to chemotactic activities of PMNs, but cysteine (10 mM) blocked this effect. The assumption was made that acrolein reacts with essential cellular protein thiol groups involved in chemotaxis, but not with proteins involved with cellular energy release such as glucose metabolism. Inhibition of human lung lactate dehydrogenase by acrolein has been demonstrated by Schabort (1967). Acrolein increaseed the permeability of human lung fibroblasts due to damage to the membrane (Thelestam et al. 1980). Wildenauer and Oehlmann (1982) found that binding and uptake of ^{14}C-labeled acrolein occurred with human red blood cells *in vitro* and was surprisingly high. There was a pronounced reaction with spectrin, a cytoskeletal protein, and also formation of globin dimerization products. Acrolein was also detected bound to rabbit liver microsomes.

In an isolated smooth muscle system from Wistar rat vas deferens, acrolein produced an irreversible contractile response (Beckner et al.,

1974). In companion studies using rabbit aorta to observe ^{45}Ca binding, acrolein affected nonspecific membrane calcium binding sites. It was concluded that acrolein may cause irreversible contraction of smooth muscle by altering membrane continuity, affecting Ca^{++} levels, which in turn affect muscle contraction. The effects of acrolein on the adrenal cortical response of rats were not inhibited by pretreatment with phenobarbital and were partially inhibited by dexamethasone (Szot and Murphy, 1970). Pretreatment of rats with acrolein increased sensitivity to various anaesthetics such as hexobarbital, pentobarbital (Jaeger and Murphy, 1973) and 2,2,2-trifluroethanol vinyl, ethyl and allyl ethers, which was due to effects on cytochrome P-450 (Murphy et al., 1983).

Warholm et al. (1984) found that a single i.p. injection of 4 mg/kg in mice caused a 5-fold increase in plasma lactate dehydrogenase (LDH) peaking after 10 hours; repeated injections produced tolerance and a less pronounced effect on LDH levels. Pretreatment of animals at this level (4 mg/kg/day) for 5 days, increased the LD_{50} (i.p.) from 7 to 12 mg/kg. Spleen, adrenals and thymus were affected histologically. Adrenalectomy decreased thymus atrophy and affected tolerance to acrolein. No change was observed in glutathione levels (GSH), but the rate of GSH synthesis was increased. In a paw edema assay in rats, acrolein caused a rapid effect which was proportional to dosage over a range of 0.5-2.5 µmole (Whitehouse and Beck, 1975). Effective "antidotes" to the irritating effect of acrolein were N-acetylcysteine, bisulphite ions and penicillamine, but sodium thiosulphate was ineffective. Other effective substances were glutathione, α-mercaptopropionylglycine, 2-mercaptoethanol and β,β-di-methylcysteamine. Incubation of splenic lymphocytes from inbred rats (male Lewis) tagged with ^{51}Cr in <50 µM acrolein drastically reduced the capacity of lymphocytes to migrate

to lymph nodes after injection of the cells into syngeneic animals. Cells not exposed to acrolein were unaffected in their node-homing abilities. Coincubation of the cells with N-acetylcysteine prevented the effect of acrolein.

Chung et al. (1984) investigated the products formed after reaction of acrolein with deoxyguanosine at pH 7 and 37° C. Cyclic 1,N^2-propanodeoxyguanosine adducts (3 major products) were formed, showing that under physiological conditions, acrolein can modify DNA by forming these cyclic adducts. Since the 1 and N^2 positions of guanine are involved in DNA base-pairing, replication may be affected and could result in mutations in cells affected by acrolein.

In a Russian study (Gusev et al., 1967) inhalation of acrolein vapors (0.51-1.52 mg/m^3) by unspecified species caused decreased cholinesterase and porphyrin and increased blood white cell counts. Except for an increase in white cell count a concentration of 0.15 mg/m^3 caused no adverse effect.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

There are considerable data available regarding the toxic responses of aquatic organisms exposed to acrolein. The acute toxicity of acrolein to 13 species of fish and 5 species of invertebrates is summarized in Tables 6-1 and 6-2.

The 24-hour static median LC_{50} of 0.062 mg/ℓ aqualin (active ingredient - 85% acrolein) to the bowfin Amia culva was established by Louder and McCoy (1962). St. Amant et al. (1964) reported 100% mortality of goldfish (Carassius auratus) exposed to aqualin in a static test at 1.0 mg/ℓ for 3 hours and a saltwater flowthrough test at 2.0 mg/ ℓ for 24 hours. Concentrations of aqualin in solution were monitored throughout the exposure by a colorimetric method. Jordan et al. (1962) exposed goldfish to nominal concentrations of acrolein in holding ponds and reported a 24-hour LC_{50} value of 2.0 mg/ℓ. Inadequate mixing of compound was reported as the probable cause of the unrealistically high LC_{50} values, and the results should be interpreted with caution. In a more standardized 24-hour static toxicity test, Bridie et al. (1979b) reported an LC_{50} value of <0.06 mg/ℓ. Louder and McCoy (1962) investigated the toxic response of fathead minnows (Pimephales promelas) exposed to acrolein in static test chambers maintained at 21.5°C. The 24- and 48-hour LC_{50} values were 0.15 and 0.115 mg/ℓ, respectively. Macek et al. (1976) determined the incipient median tolerance limit (TLM) of fathead minnows exposed to acrolein at 25°C in a flowthrough system to be 0.084 mg/ℓ for 114 hours. Juhnke and Luedemann (1978) reported a 10-fold variation in the LC_{50} values of 0.25 and 2.5 mg/ℓ established for the golden orfe (Leuciscus idus melanotus) at two independent laboratories; descriptions of protocol and discussion of variation in results were not provided.

TABLE 6-1

Acute Lethal Effects of Acrolein on Fresh and Saltwater Fish

Species	Duration (hours)	Concentration (mg/L)	Method	Effect	Reference
Sea lamprey larvae (*Petromyzon marinus*)	24	5.0	13°C; static	no response	Applegate et al., 1957
Bowfin (*Amia calva*)	24	0.062	21.5°C; static	LC_{50}	Louder and McCoy, 1962
Goldfish (*Carassius auratus*)	24	<0.06	20°C; static	LC_{50}	Bridie et al., 1979b
	24	2.0	field pond; nominal	LC_{50}	Jordan et al., 1962
	3	1.0	static	100% mortality	St. Amant et al., 1964
	24	2.0	flowthrough; saltwater	100% mortality	St. Amant et al., 1964
Fathead minnow (*Pimephales promelas*)	24	0.15	21.5°C; static	LC_{50}	Louder and McCoy, 1962
	48	0.115	21.5°C; static	LC_{50}	Louder and McCoy, 1962
	114	0.084	25°C; flowthrough	incipient TL_m	Macek et al., 1976

TABLE 6-1 (Cont.)

Species	Duration (hours)	Concentration (mg/l)	Method	Effect	Reference
Golden orfe (Leuciscus idus melanotus)	NR	0.25	NR	LC_{50}	Juhnke and Luedemann, 1978
	NR	2.5	NR	LC_{50}	Juhnke and Luedemann, 1978
Rainbow trout (Salmo gairdneri)	24	0.14	flowthrough	LC_{50}	Folmar, 1976
	24	0.065	20°C; static	LC_{50}	Bond et al., 1960
	24	5.0	13°C; static	no observed toxic effect	Applegate et al., 1957
Brown trout (Salmo trutta)	24	0.046	15.5°C; flowthrough	LC_{50}	Burdick et al., 1964
Chinook salmon (Oncorhynchus tshawytscha)	2	1.35	20°C; static	100% mortality	Bond et al., 1960
Coho salmon (Oncorhynchus kisutch)	96	0.068	10°C; static	LC_{50}	Lorz et al., 1979

TABLE 6-1 (cont.)

Species	Duration (hours)	Concentration (mg/l)	Method	Effect	Reference
Bluegill (Lepomis macrochirus)	24	0.08	20°C; static	LC_{50}	Bond et al., 1960
	24	0.10	22°C; static	LC_{50}	Buccafusco et al., 1981
	96	0.09	22°C; static	LC_{50}	Buccafusco et al., 1981
	24	0.14	21.5°C; static	LC_{50}	Louder and McCoy, 1962
	96	0.10	21.5°C; static	LC_{50}	Louder and McCoy, 1962
	24	0.077	60°F; flowthrough	LC_{40}	Burdick et al., 1964
	24	2.0	field pond; nominal	LC_{50}	Jordan et al., 1962
	96	0.09	NR	LC_{50}	U.S. EPA, 1978b
	24	5.0	13°C; static	no response	Applegate et al., 1957
Large mouth bass (Micropterus salmoides)	24	0.183	21.5°C; static	LC_{50}	Louder and McCoy, 1962
	96	0.16	21.5°C; static	LC_{50}	Louder and McCoy, 1962

TABLE 6-1 (cont.)

Species	Duration (hours)	Concentration (mg/L)	Method	Effect	Reference
Longnose Killifish (*Fundulus similis*)	24	0.28	flowthrough; saltwater	LC_{50}	Butler, 1965
	48	0.24	flowthrough; saltwater	LC_{50}	Butler, 1965
Harlequin fish (*Rasbora heteromorpha*)	24	0.14	20°C; flowthrough	LC_{50}	Alabaster, 1969
	48	0.06	20°C; flowthrough	LC_{50}	Alabaster, 1969
Rainbow trout (*Salmo gairdneri*)	1	0.001-49% 0.01-56% 0.1-88%	NR	percent avoidance	Folmar, 1976

NA = Not applicable; NR = not reported

TABLE 6-2

Acute Lethal Effects of Acrolein on Aquatic Invertebrates

Species	Duration (hours)	Concentration (mg/l)	Method	Effect	Reference
Freshwater Species					
Water flea (Daphnia magna)	48	0.08	NR	LC_{50}	U.S. EPA, 1978b
	48	0.08	22 ± 1°C; static	LC_{50}	LeBlanc, 1980
	48	0.057	static	LC_{50}	Macek et al., 1976
Protozoan (Entosiphon sulcatum)	72	0.85	NR	LC_{50}	Bringmann, 1978
Snail eggs (Australorbis glabratus)	24	0.08	static	40% mortality	Ferguson et al., 1961
Snail adults (Australorbis glabratus)	24	0.10	static	58% mortality	Ferguson et al., 1961
Saltwater Species					
Brown shrimp (Panaeus aztecus)	24	0.19	50% mortality or	EC_{50}	Butler, 1965
	48	0.10	loss of equilibrium	EC_{50}	Butler, 1965
Oyster (Mollusca) (Crassostrea virginica)	96	0.055	21°C; 50% reduction in shell growth	EC_{50}	Butler, 1965

NR = Not reported

Folmar (1976) investigated the toxic effects and avoidance reaction of rainbow trout (Salmo gairdneri) to acrolein. A 24-hour flowthrough LC_{50} value of 0.14 mg/ℓ and an observed 56% avoidance at 0.01 mg/ℓ (see Table 6-1) were reported. Bond et al. (1960) observed similar results, LC_{50} 0.065 mg/ℓ, in a 24-hour static toxicity test with rainbow trout maintained at 20°C. The 24-hour flowthrough LC_{50} of 0.046 mg/ℓ was determined for brown trout (Salmo trutta) maintained at 15.5°C (Burdick et al. 1964). Lorz et al. (1979) established the 96-hour static LC_{50} of 0.068 mg at 10°C for coho salmon (Oncorhynchus kisutch). Complete mortality of chinook salmon (Oncorhynchus tshawytscha) was reported by Bond et al. (1960) after a 2-hour static exposure to 1.35 mg/ℓ acrolein at 20°C.

The 24-hour LC_{50} values for bluegill (Lepomis macrochirus) established by Bond et al. (1960), Buccafusco et al. (1981), Louder and McCoy (1962), and Burdick et al. (1964) are in close agreement (see Table 6-1), as are the 96-hour LC_{50} values of Buccafusco et al. (1981), Louder and McCoy (1962), and the U.S. EPA (1978b) (see Table 6-1); however, Jordan et al. (1962) reported a 24-hour LC_{50} value of 2.0 mg/ℓ for bluegill treated with acrolein in an open pond. Inadequate mixing, due to the concentration of submerged macrophytes was reported as the probable cause of the unrealistically high LC_{50} values.

Louder and McCoy (1962) investigated the toxic responses of largemouth bass (Micropterus salmoides) exposed to acrolein in a static system maintained at 21.5°C and established 24- and 96-hour LC_{50} values of 0.183 and 0.16 mg/ℓ, respectively.

Butler (1965) examined the toxicity of acrolein to a saltwater species, the longnose killifish (Fundulus similis), and established 24- and 48-hour flowthrough LC_{50} values of 0.28 and 0.24 mg/ℓ, respectively. Alabaster

(1969) conducted a similar series of investigations of the flowthrough toxicity to another saltwater species, the harlequin fish (Rasbora Heteromorpha), establishing 24- and 48-hour LC_{50} values of 0.14 and 0.06 mg/ℓ, respectively, (see Table 6-1).

Applegate et al. (1957) investigated the toxic effects of acrolein on larval sea lamprey (Petromyzon marinus), rainbow trout, and bluegill with greatly differing results, but no response was detected in any of the organisms exposed to concentrations up to 5.0 mg/ℓ. No discussion of the results was provided.

The 48-hour LC_{50} values of 0.08, 0.08, and 0.057 mg/ℓ acrolein to the water flea (Daphnia magna) were established during the investigations of LeBlanc (1980), U.S. EPA (1978b) and Macek et al. (1976), respectively (see Table 6-2). Bringmann (1978) determined the 72-hour LC_{50} for the protozoan Entosiphon sulcatum to be 0.85 mg/ℓ, or 10 times greater than the LC_{50} for the waterflea. Ferguson et al. (1961), investigating the effects of acrolein on snails (Australorbis glabratus), reported that concentrations of 0.08 and 0.10 mg/ℓ caused 40% mortality in eggs and 58% mortality in adults, respectively.

Butler (1965) calculated the 24- and 48-hour median effective concentration (EC_{50}) values, the concentration necessary to cause mortality or loss of equilibrium in 50% of the organisms, of 0.19 and 0.10 mg/ℓ, respectively, for the saltwater brown shrimp (Panaeus aztecus). He also calculated the concentration necessary to cause a 50% reduction in shell growth, the 96-hour EC_{50} value to be 0.055 mg/ℓ for the salt water oyster, Crassostrea virginica.

6.2. CHRONIC TOXICITY

The maximum acceptable toxicant concentration (MATC) value of 0.011 mg/ℓ acrolein was established for the fathead minnow by Macek et al. (1976) in a flowthrough study maintained at 25°C (Table 6-3).

6.3. PLANT EFFECTS

Data regarding the responses of aquatic plants exposed to acrolein were limited. Van Overbeek et al. (1959) reported that concentrations of 0.5 and 5.0 mg/ℓ acrolein applied to Elodea sp. were sufficient to destroy all viable cells within 24 and 2 hours, respectively (see Table 6-3).

6.4. RESIDUES

A maximum bioconcentration factor of 344 (see Table 6-3) was established within 28 days of exposure for the bluegill (Barrows et al., 1980).

6.5. OTHER RELEVANT INFORMATION

Additional data regarding the toxic effects of acrolein to aquatic organisms were not located in the available literature as cited in the Appendix.

TABLE 6-3

Chronic Toxicity and Bioaccumulation of Acrolein to Aquatic Organisms

Species	Duration	Concentration (mg/l)	Method	Effect	Reference
Fathead minnows (Pimephales promelas)	NR	0.011	25°C; flowthrough	MATC	Macek et al., 1976
Bluegill (Lepomis macrochirus)	28 days	344 (maximum)	NR	BCF	Barrows et al., 1980
Elodea sp.	24 hours	0.5	aquaduct treatment	100% cell mortality	Van Overbeek et al., 1959
	2 hours	5.0	aquaduct treatment	100% cell mortality	Van Overbeek et al., 1959

NR = Not reported

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The ACGIH (1984) adopted a TWA-TLV of 0.1 ppm (0.25 mg/m³) for acrolein and a STEL of 0.3 ppm (0.8 mg/m³). The TLV is considered to be sufficiently low to minimize, but not to prevent, irritation to mucous membranes (ACGIH, 1980)

OSHA adopted the same TLV of 0.1 ppm (0.25 mg/m³) (CFR, 1981). Kane and Alarie (1977) concluded that 0.1 ppm is acceptable but close to the high limits of the acceptable range (U.S. EPA, 1980). Based on Russian studies Gusev et al. (1967) reported a maximal permissible concentration of acrolein of 0.1 mg/m³ .

The U.S. EPA (1980) determined an ADI for humans of 15.6 µg/kg or 1.09 mg/day for a 70 kg man. This corresponds to an ADI in drinking water of 0.32 mg/ℓ for acrolein. The ADI was based on the study of Newell (1958) in which no effects were observed in rats treated at drinking water levels of ≤200 mg/ℓ for 90 days.

7.2. AQUATIC

The available data for acrolein indicate that acute and chronic toxicity to freshwater aquatic life occur at concentrations as low as 0.046 and 0.011 mg/ℓ, respectively and that acute toxicity to saltwater aquatic life occurs at concentrations as low as 0.055 mg/ℓ; however, these effects would occur at lower concentrations among species that are more sensitive than those tested.

8. RISK ASSESSMENT

The 52-week study by Feron and Kruysse (1977), in which hamsters were exposed to inhaled acrolein at a concentration of 9.2 mg/m^3, presents no clear evidence for carcinogenicity. Using U.S. EPA's (1984) weight of evidence classification system acrolein would be classified in Group D, reflecting an inadequate data base for the evaluation of carcinogenic potential. Results of mutogenicity testing are equivocal (see Table 5-2).

Teratology studies of acrolein administered to pregnant rats by the oral or inhalation routes were not available. Intravenous injection of pregnant rabbits on day 9 of gestation resulted in dose-related increased incidences of fetal deaths and malformations at $\geq$3 mg/kg (Claussen et al., 1980). Retarded growth, malformations and death of embryos were also observed in studies in which explanted animal embryos were cultured with acrolein *in vitro* or acrolein was injected intrauterinely directly into the amniotic fluid or yolk sac (Hales, 1982; Claussen et al., 1980; Schmid et al., 1981; Stahlman et al., 1981; Mirkes et al., 1981; Spielmann and Jacob-Mueller, 1981). It should be noted that studies conducted *in vitro* or by direct injection into the uterus may not reflect the reponse obtained after administration of acrolein by a natural route.

Subchronic and chronic inhalation exposure of a variety of species to acrolein has been associated with such effects as reduced body weight gain, inflammation, hyperplasia and metaplasia of the respiratory tract epithelium, inflammatory changes in the liver, kidney and spleen, and hematological effects (Bouley et al., 1975, 1976; Philippin et al., 1969; Lyon et al., 1970; Feron et al., 1978; Feron and Kruysse, 1977; Kutzman et al., 1984). Effects were observed at inhalation exposures as low as 0.5 mg/m^3

continuously for 90 days, or 0.92 mg/m³, 6 hours/day, 5 days/week for 62 days (see Section 5.5); therefore, a NOAEL for inhalation exposure cannot be defined.

The only available oral study using acrolein, Newell (1958), was summarized by NAS (1977). In this study, acrolein was added to drinking water of rats at concentrations of 5, 13, 32, 80 and 200 mg/ℓ for 90 days. In a second experiment, death from lack of water intake was observed at concentration $\geq$600 mg/ℓ for 60 days. No adverse effects were observed in hematologic, organ-weight, or histopathologic parameters. The only effect observed was decreased water ingestion by the rats. This study was selected by the U.S. EPA (1980) to calculate an ADI. Assuming that daily water consumption by a rat is equal to 7.8% of the body weight, the dosage of 15.6 mg/kg/day for rats exposed to 200 mg/ℓ was calculated. This study involved subchronic exposure of 90 days, so an uncertainty factor of 1,000 was applied: a factor of 10 for subchronic duration; a factor of 10 for species extrapolation; and a factor of 10 for interindividual variability. Dividing the value of 15.6 mg/kg by the uncertainty factor of 1000 resulted in a value of 0.0156 mg/kg/day or 1.09 mg/day for a 70 kg individual. Because no additional data regarding the effects of long-term oral exposure of animals to acrolein have become available, the ADI of 1.09 mg/day is recommended to protect humans. Since acrolein has not been tested adequately for carcinogenicity or teratogenicity by the oral route, the proposed value should be reevaluated as additional data become available.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Subchronic inhalation studies in several species define effects which are relevent to RQ development. The sole oral study, Newell (1958) did not define effect levels. Table 9-1 summarizes the relevent inhalation studies and the associated estimated doses in units of mg/kg/day. These doses were estimated using either default values ror body weight and ventilatory volumes (U.S. EPA, 1980, 1985) or when body weight data were provided by the authors, ventilatory volumes for the animals were estimated utilizing species specific algorithms relating body weight to ventilatory volume (U.S. EPA, 1980, 1985).

Human MEDs in units of mg/day were calculated from animal mg/kg doses by multiplying by the cube root of the body weight ratio (animal: human) and subsequently multiplying by 70 kg. These MEDs were divided by an additional factor of 10 to adjust for subchronic exposure duration. MEDs and composite scores are shown in Table 9-2. The composite scores developed for several species and strains agree remarkably well. The highest composite score, 40.8 is developed for two independent studies using different strains of rats and a third study using squirrel monkeys. This CS is associated with an RQ of 10 pounds and is summarized in Table 9-3.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Within the limits of the studies available in the literature, acrolein has not been found to be a carcinogen, although it should be kept in mind that the number of studies presented are small. The data are insufficient to allow any conclusion regarding carcinogenic effects to humans from exposure to acrolein.

TABLE 9-1

Toxicity Summary for Acrolein

Route	Species/ Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
Oral	rat	NR	NR	0.35[a]	water/ liquid	NR	≤200 mg/L for 90 days	≤28	No effect, slight weight reduction due to unpalatability of drinking water	Newell, 1958
Inhalation	rat	NR	15	0.35[a]	air/ vapor	NR	1.27 mg/m³ for 77 days, continuously	0.81	Respiratory tract and nasal irritation, respiratory tract disorders, transitory hepatic enzyme effect (serum acid phosphatase)-all disappearing after 3 weeks. Lowered food consumption and weight gain	Bouley et al., 1975; 1976
Inhalation	rat/ Sprague Dawley	7 M 8 F	15/group	0.43[b] (M) 0.30[b] (F)	air/ vapor	highest commercial redistilled	2,3 and 4.1 mg/m³ continuously for 90 days	1.4 and 2.4 (M) 1.5 and 2.8 (F)	Inflammation of the brain, heart, lung, liver, kidney; decreased weight gain ($p<0.005$); lung metaplasia and hyperplasia; occasional pulmonary hemorrhage; eye irritation; focal liver necrosis or minute foci	Lyon et al., 1970
Inhalation	rat/ Sprague Dawley	7 M 8 F	15	0.43[b] (M) 0.30[b] (F)	air/ vapor	highest commercial redistilled	1.6 mg/m³ for 8 hours/day, 5 days/week for 6 weeks	0.23 (M) and 0.26 (F)	Chronic lung inflammatory changes	Lyon et al., 1970
Inhalation	rat/ Sprague Dawley	7 M 8 F	15	0.43[b] (M) 0.30[b] (F)	air/ vapor	highest commercial redistilled	8.5 mg/m³ for 8 hours/day, 5 days/week for 6 weeks	1.2 (M); 1.4 (F)	Decreased weight gain ($p<0.005$) for both males and females; inflammatory changes in lung, liver and kidney	Lyon et al., 1970
Inhalation	rat/ Sprague Dawley	15 M 15 F	15/group	0.43[b] (M) 0.30[b] (F)	air/ vapor	highest commercial redistilled	0.5 mg/m³ continuously for 90 days	0.30 (M); 0.3 (F)	No effect	Lyon et al., 1970
Inhalation	rat/ Sprague Dawley	M and F	12	0.43[b] (M) 0.30[b] (F)	air/ vapor	freshly prepared	11.3 mg/m³ for 6 hours/day, 5 days/week for 13 weeks	1.5 (M); 1.8 (F)	Eye irritation, decreased food consumption and weight gain, histopathological changes in the respiratory tract	Feron et al., 1978

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
Inhalation	rat/	M and F	12	0.23[b] (M) 0.13[b] (F)	air/ vapor	freshly prepared	3.2 mg/m³ for 6 hours/day, 5 days/week for 13 weeks	0.42 (M); 0.5 (F)	Decreased body weight gain, squamous metaplasia and neutrophilic infiltration of nasal mucosa	Feron et al., 1978
Inhalation	rat/	M and F	12	0.23[b] (M) 0.13[b] (F)	air/ vapor	freshly prepared	0.92 mg/m³ for 6 hours/day, 5 days per week for 13 weeks	0.12 (M); 0.15 (F)	Slight growth depression, histopathological changes in nasal cavity (metaplasia), slight decrease in kidney and testicular weight	Feron et al., 1978
Inhalation	rat/ Dahl (DS)[c]	F	10	0.15[b]	air/ vapor	NR purchased as 1000 ppm in N_2	9.2 mg/m³ for 6 hours/day, 5 days/week for 62 days	1.4 kg	Pulmonary edema, proliferation of lung connective tissue, airway epithelial necrosis and hemorrhage death in 11 days for all	Kulzman et al., 1984
Inhalation	rat/ Dahl (DR)[c]	F	10	0.15[b]	air/ vapor	NR purchased as 1000 ppm in N_2	9.2 mg/m³ for 6 hours/day, 5 days/week for 62 days	1.4 kg	71% increase serum alkaline phosphatase, lung proliferation changes and multifocal interstitial pneumonitis; heart, liver, brain weight increase; only 4/10 dead after 62 days, lung-to-body weight ratio increased	Kulzman et al., 1984
Inhalation	rat/ Dahl (DR)[c] and (DS[c])	F	10 per strain per group	0.15[b]	air/ vapor	NR purchased as 1000 ppm in N_2	0.92 and 3.2 mg/m³ for 6 hours/day, 5 days/week for 62 days	0.14 and 0.48	Lung inflammatory response, bronchiolar epithelial hyperplasia and macrophage clusters at both dosage levels	Kulzman et al., 1984
Inhalation	mice	NR	NR	0.03[b]	air/ vapor	NR	13.8 and 34.5 mg/m³ for 6 hours/day, 5 days/week for 6 weeks	3.2 and 8.0	Small decrease in body weight	Phillppin et al., 1969
Inhalation	mouse	M	5	0.02[b]	air/ vapor	NR	100 mg/m³ for 30 minutes, twice a day for 5 weeks	6.2	Reduction in pulmonary compliance	Watanabe and Aviado, 1974

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
Inhalation	guinea pig/ Prince-	15 M 15 F	15 for each exposure	0.612[b]	air/ vapor	highest Commercial redistilled	0.50 mg/m³ for 90 days	0.24 (M); 0.25 (F)	No effect except inflammatory changes in liver lung, kidney, heart	Lyon et al., 1970
Inhalation	dog/ beagle	M	2	11.7[b]	air/ vapor	highest commercial redistilled	8.5 mg/m³ for 8 hours/ day, 5 days/ week for 6 weeks	0.69	Eye irritation, breathing difficulty, broncho-pneumonia, squamous metaplasia and basal cell hyperplasia of trachea, lung, liver and kidney inflammatory changes	Lyon et al., 1970
Inhalation	dog/ beagle	M	2	11.7[b]	air/ vapor	highest commercial redistilled	1.6 mg/m³ for 8 hours/ day, 5 days/ week for 6 weeks	0.13	Lung inflammatory	Lyon et al., 1970
Inhalation	dog/ beagle	M	2 (4)	11.7[b]	air/ vapor	highest commercial redistilled	0.50 mg/m³ continuously for 90 days	0.17	Histological lung changes, splenic focal subcapsular hemorrhage, hyperplasia of thyroid gland, inflammatory changes liver, lung, kidney, heart	Lyon et al., 1970
Inhalation	dog/ beagle	M	2	11.7[b]	air/ vapor	highest commercial redistilled	2.2 mg/m³ continuously for 90 days	0.75	Focal inflammatory reactions in lung, kidney and liver one dog had broncho-pneumonia, ocular and nasal discharge	Lyon et al., 1970
Inhalation	dog/ beagle	M	2	11.7[b]	air/ vapor	highest commercial redistilled	4.1 mg/m³	1.4	Excessive salivation and ocular discharge, tracheal changes, inflammatory changes brain, heart, lung, liver, kidney; broncho-pneumonia	Lyon et al., 1970
Inhalation	monkey/ squirrel	M	9	0.623[b]	air/ vapor	highest commercial redistilled	8.5 mg/m³ for 8 hours/ day, 5 days/	0.49	Eye irritation, squamous metaplasia of lung, necrotizing bronchitis and bronchiolitis; squamous metaplasia and basal cell hyperplasia of tracheal; two monkeys died, one on day 6, one on day 9; lung, liver, kidney inflammatory	Lyon et al., 1970

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
Inhalation	hamsters	M and F	20	0.14[b]	air/ vapor	freshly prepared	11.3 mg/m³ for 6 hours/day 5 days/week for 13 weeks	1.9	Eye irritation, decreased weight and food consumption, respiratory tract histopathological changes, increased lung heart and kidney weight statistically significant increase in erythrocyte number, hematocrit and lymphocyte number and decreased neutrophils	Feron et al., 1978
Inhalation	hamsters	M and F	20/group	0.14[b]	air/ vapor	freshly prepared	3.2 and 0.92 mg/m³ for 6 hours/day, 5 days/week for 13 weeks	0.53 and 0.15	No effect	Feron et al., 1978
Inhalation	hamsters	M F	36 36	0.095[b] 0.105[b] (F)	air/ vapor	freshly prepared	9.2 mg/m³ for 7 hours/day 5 days/week for 52 weeks	1.8 (M,F)	Growth retardation; increased hemoglobin, packed cell volume, and relative lung weight (in females); decreased liver weight, (in females); metaplasia of nasal cavity accompanied by rhinitis	Feron and Kruysse, 1977
Inhalation	rabbits	M and F	4	1.8[b]	air/ vapor	freshly prepared	11.3 mg/m³ for 6 hours/day 5 days/week for 13 weeks	1.1	Histopathological changes in respiratory tract, eye irritation, decreased food consumption and weight gain, increased relative lung weight	Feron et al., 1978
Inhalation	rabbits	M and F	4 per exposure level	1.8[b]	air/ vapor	freshly prepared	0.92 and 3.2 mg/m³ for 6 hours/day, 5 days/week for 13 weeks	0.09 and 32	No effect at 0.92 mg/m³ decreased body weight gain	Feron et al., 1978
Inhalation	guinea pig/ Princeton or Hartley	7 M 8 F	15 for each	0.612[b] (M) 0.539[b] (F)	air/ vapor	highest commercial	2.3 and 4.1 mg/m³ continuously for 90 days	1.1 and 2.0 (M); 1.1 and 2.0 (F)	Pulmonary inflammation, occasional foci of liver necrosis, inflammatory changes liver, lung, kidney, heart, brain	Lyon et al., 1970

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
Inhalation	monkey/ squirrel	M	9	0.623[b]	air/ vapor	highest commercial redistilled	1.6 mg/m³ for 8 hours/ day, 5 days/ week for 6 weeks	0.09	Chronic lung inflammation and occasional emphysema	Lyon et al., 1970
Inhalation	monkey/ squirrel	M	9	0.623[b]	air/ vapor	highest commercial redistilled	0.50 mg/m³ continuously for 90 days	0.121	Nonspecific inflammatory changes liver, lung, kidney, heart	Lyon et al., 1970
Inhalation	monkey/ squirrel	M	9	0.623[b]	air/ vapor	highest commercial redistilled	2.2 mg/m³ continuously for 90 days	0.53	One monkey died on day 28 due to bite; excessive salivation and ocular discharge, several organs had inflammation	Lyon et al., 1970
Inhalation	monkey/ squirrel	M	9	0.623[b]	air/ vapor	highest commercial redistilled	4.1 mg/m³ continuously for 90 days	0.99	Excessive salivation and ocular discharge, non-specific inflammatory changes in the brain, heart, lung, liver and kidney; squamous metaplasia and basal cell hyperplasia of trachea (6/9)	Lyon et al., 1970

[a]Average body weight assumed

[b]Average body weight estimated from weight gain data provided by investigators

[c]DS refers to a salt-inducted hypertension sensitive strain; DR refers to a resistant strain

NR = not reported

M = Male

F = Female

TABLE 9-2

Inhalation Composite Scores for Acrolein

Species	Animal Dose (mg/kg)	Chronic Human MED* (mg/kg)	RV_d	Effects	RV_e	CS	RQ	Reference
Rat	0.12	0.14	6.8	Metaplasia and nasal cavity inflammation	6	40.8	10	Feron et al., 1978
Mouse	6.2	2.9	4.8	Reduced pulmonary compliance	7	33.6	100	Watanabe and Aviado, 1974
Rat	0.81	0.97	5.5	Respiratory disorders	7	38.5	100	Bouley et al., 1975, 1976
Rat	1.5	1.7	5.2	Lung metaplasia, liver necrosus	7	36.4	100	Lyon et al., 1970
Rat	0.14	0.13	6.8	Lung inflammation, hyperplasia	6	40.8	10	Kutzman et al., 1984
Guinea pig	0.25	0.35	6.2	Inflammatory change, lung, liver, heart	6	37.2	100	Lyon et al., 1970
Dog	0.69	2.7	4.9	breathing difficulty	8	39.2	100	Lyon et al., 1970
Monkey	0.09	0.13	6.8	Lung inflammation	6	40.8	10	Lyon et al., 1970
Monkey	0.121	0.18	6.6	Inflammatory changes liver, lung, kidney, heart	6	39.8	100	Lyon et al., 1970

*Divided by a factor of 10 to approximate chronic exposure

TABLE 9-3

Acrolein
Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose[a]:	0.13 mg/day
Effect:	inflammation of respiratory tract
Reference:	Lyon et al., 1970; Kutzman et al., 1984; Feron et al., 1978
RV_d:	6.8
RV_e:	6
Composite Score:	40.8
RQ:	10

[a]Equivalent human dose

Acrolein is most appropriately placed in IARC Group 3, (U.S. EPA Category D) as a chemical that cannot be classified as yet as to its carcinogenicity for humans.

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Appendix

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in February, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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